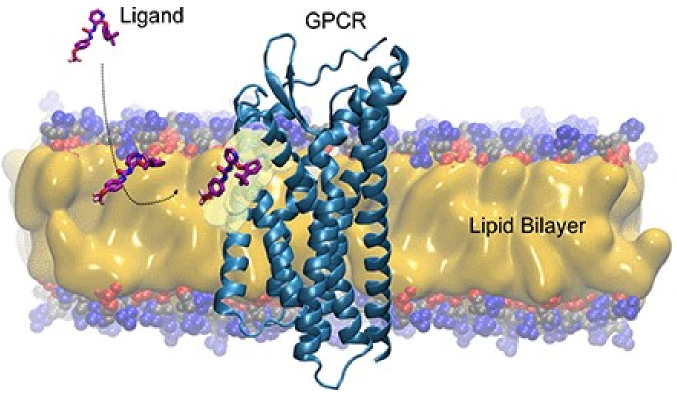

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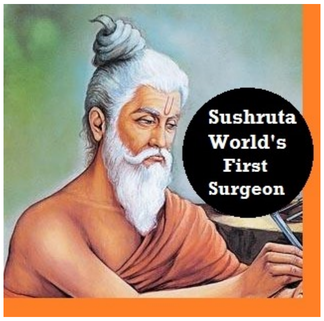

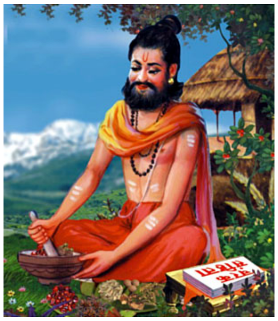

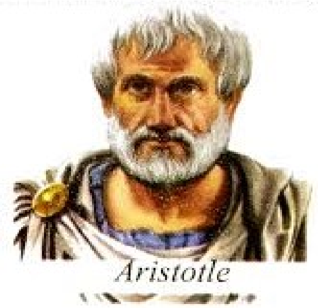

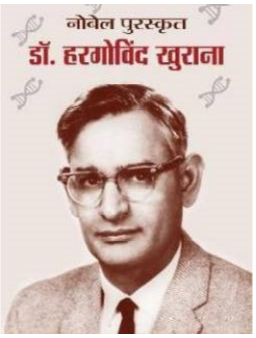

B.Sc. ZOOLOGY - Sem. I

Course Code: B050101T

PROF. RAJENDRA SINGH (RAJJU BHAIYA) UNIVERSITY, PRAYAGRAJ, UTTAR PRADESH

Cytology, Genetics and Infectious Diseases

Up to the Syllabus of National Education Policy-2020

UNIT - I

Structure and Function of Cell Organelles I

And

Important national (Vedic and Ancient) and international Biologists (Zoologists) who have contributed/contributing to Zoological and Life Sciences

BY

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PREFACE

The state universities of Uttar Pradesh have been regularising the syllabus according to the New Education Policy, 2020. The new syllabus of zoology is advanced for the countryside students and seems to be hard to understand the some topics of cell biology and genetics that have been allotted to the first semester students. The authors have tried to explain these complicated topics in easy languages without changing the basic concepts and recent advancement of related topics. The writings of this book have been based on the literature of research papers and international master books of related subjects. The aim of this eBook is to outreach the countryside students through Google platform. The interested students of our country side will surely increase their knowledge in zoology by reading this book. The further topics of B.Sc. Semester I will be added in response to the reader students.

AUTHORS

Chapter 1

Plasma Membrane - its existence in nature

All living organisms are made of microscopic cells that are separated with each other by a extremely thin membrane called a **Plasma Membrane** (PM) or in other words an outermost layer of a cell that encircles its living substance and protoplasm, **Figure 1**. The plasma membrane is also known as the **Cell membrane** or **Cytoplasmic membrane**, and historically referred to as the **Plasmalemma**. Various biological functions performed by the PM like interaction to other cells, anchoring to substrates, secretion of proteins, ingestion of foods, shape and sizes including protection. Overall, PM makes the cell to work coordinately with other cells of the body

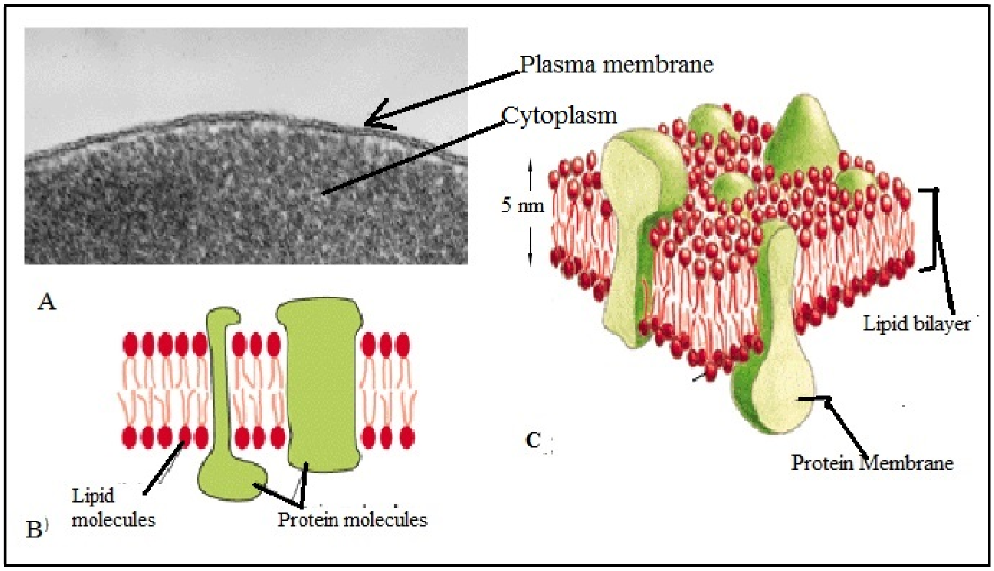


Figure 1 Three views of a cell membrane. (A) An electron micrograph of a plasma membrane (of a human red blood cell) seen in cross-section. (B and C) Schematic drawings showing twodimensional and three-dimensional views of a cell membrane. *Source – Alberts et al.*

The plasma membrane is made up of two layers of lipids (fats) that are known as bilayers (**Figure 1**). Both the layers in animal cells are composed largely of **lipids**, **protein** and **carbohydrates** that are at some times also pronounced as lipid membranes and that are physically soft, elastic, fragile and dynamic in nature. Whereas, cell membranes in plants are made of Cellulose (a type of carbohydrates) that becomes hard on dry as wood in nature. Similarly, bacteria, fungi and algae other protists also have a membrane referred to as the ***prokaryotic cytoplasmic membrane***. Plasma membranes are very thin that usually range from **5 to 10 nm in thickness**. But in the case of human red blood cells comparatively thicker (approximately 8 µm wide, or approximately 1,000 times wider than a plasma membrane) that can be easily visible under light microscopy.

Indeed, studies of plasma membrane of the red blood cell provided the first evidence that biological membranes consist of lipid bilayers (**Figure 1**). The biologists are also using it for experimental study due to its thickness, easily availability and absences of nuclei or internal membranes. The eukaryotic cell organelles such as nucleus, endoplasmic reticulum, Golgi bodies, mitochondria and plastids are also made up of bilayer plasma membrane whereas lysosomes, endosomes and vacuoles are referred as single - membrane organelles. Another example of plasma membranes can be internal membranes of hen's egg if it can be separated.

Chemical structure—lipids and proteins

The cell membrane is composed mainly of various types of **lipids (fats)**, **protein**, and a **small percentage of oligosaccharides (carbohydrates)** that may be attached to either the lipids (glycolipids) or the proteins (**glycoproteins**).

1. Lipids

The cell membrane contains about 20 to 79% of lipid. The main lipid constituents of cell membranes are **phospholipids**, **cholesterol** and **galactolipids**; their proportions vary in different cell membranes. Membrane lipids are amphipathic, which means that they have a polar or hydrophilic end and a non-polar or hydrophobic end. Membrane lipids are highly diverse, with a typical membrane containing more than 100 species of lipids. These lipids vary in their structure and extent of saturation of the fatty acyl chains. There are three major classes of membrane lipids – the **phosphoglycerides**, **sphingolipids** and **sterols**.

Phospholipids

The phosphoglycerides and sphingolipids can be combined as one class, the phospholipids. These are the classical membrane lipid, formed of a polar head group and two hydrophobic fatty acid tails **Figure 1.1**. The fatty acid tails typically contain between 14-24 carbon atoms. One of the two tails is unsaturated and therefore contains one or more cis-double bonds, which creates a small kink in the tail. The other tail is saturated, without any cis-double bonds and remains straight. Variations in the length and saturation of the fatty acid tail affect how tightly phospholipids are able to pack against each other, leading to altered membrane fluidity. Saturated fatty acids have no double bonds in the hydrocarbon chain, and the maximum amount of hydrogen. The absence of double bonds decreases fluidity, making the membrane very strong and stacked tightly. The natural source of **unsatutated** faty acid are oils and **saturated fatty** are animal fats i.e. Ghee. These double bonds are not statics but dynamics according to temperature and also play crucial role in temperature

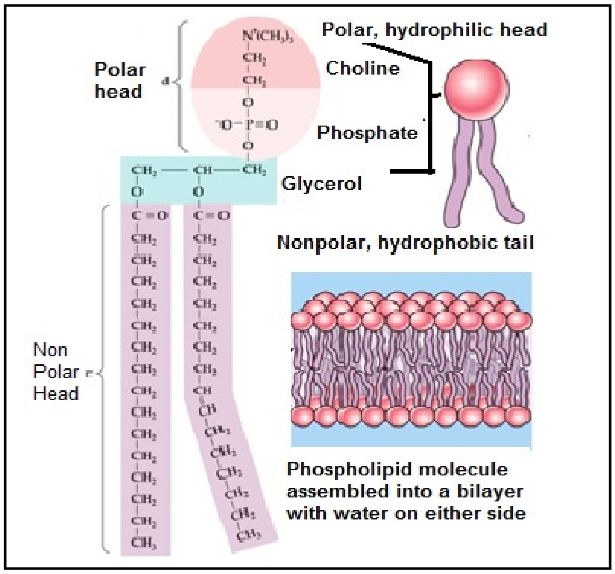
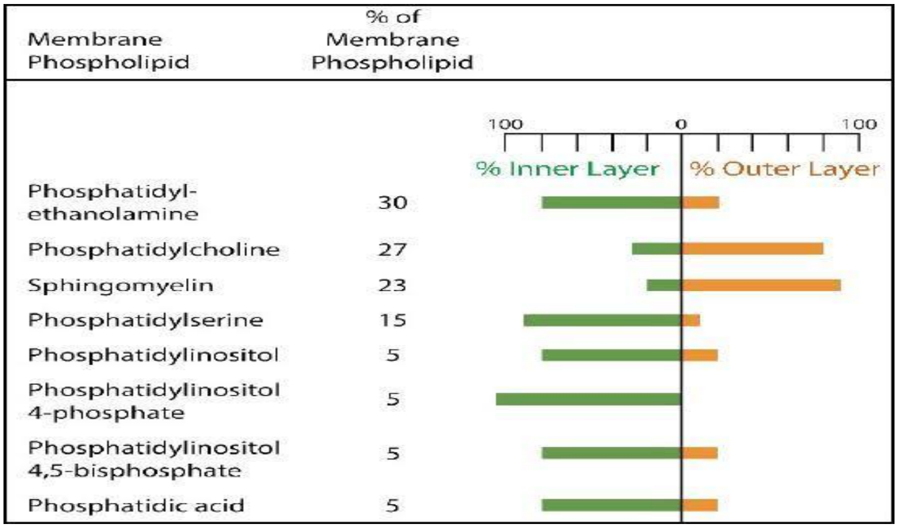


Figure 1.1 A typical model structure of a phosolipid choline and its assamble in bilayer lipid

Similarly when Ghee is heated, it converts by forming more double bonds, into fluid like oil and on reversing it again turned into fat by losing double bond. The polar head group to the fatty acid tail is a backbone made up of either glycerol or sphingosine. The different backbone molecule differentiates between the classes of phospholipid. Phosphoglycerides have a polar head group esterified to one of three glycerol hydroxyl groups, and two hydrophobic fatty acid tails esterified to the remaining two hydroxyl groups of the glycerol backbone. The polar head group is composed of a phosphate group linked to choline, ethanolamine, serine or inositol. These form phosphatidyl choline (PC), phosphatidyl ethanolamine (PE), phosphatidyl serine (PS) and phosphatidylinositol (PI) respectively. Sphingolipids, on the other hand, have a backbone formed from sphingosine, an amino alcohol with a long hydrocarbon chain; a less abundant class of membrane lipids. Ceramide is a simple sphingolipid which has a hydrophobic fatty acid tail linked to the amino group of the sphingosine

Table 1 Representation of different types of lipids molecules and their typical occurrence inner and outer side in percentages.



Membrane Phospholipid	% of Membrane Phospholipid
Phosphatidyl-ethanolamine	30
Phosphatidylcholine	27
Sphingomyelin	23
Phosphatidylserine	15
Phosphatidylinositol	5
Phosphatidylinositol 4-phosphate	5
Phosphatidylinositol 4,5-bisphosphate	5
Phosphatidic acid	5

The esterification of additional groups to the terminal hydroxyl group of the sphingosine backbone gives rise to other types of sphingolipids. For instance, sphingomyelin has a polar phosphoryl choline head group and glycolipids have a carbohydrate group. The carbohydrate group of glycolipids can be a simple sugar or an oligosaccharide forming cerebrosides and gangliosides respectively **Table 1**.

Sterols

These are smaller than phospholipids. They have a single polar hydroxyl head group attached to a rigid steroid ring structure and a short non-polar hydrocarbon tail. Cholesterol is the major sterol component of animal cell membranes. Different sterols are found in other eukaryotic cell membranes.

Yeast and fungi use ergosterol, while plants use sitosterol and stigmasterol. However, prokaryotic cell membranes essentially contain no sterols. Sterols insert into the lipid bilayer with their hydroxyl head groups oriented with the phospholipid polar groups.

This aligns the rigid ring structure of the sterol with the phospholipid hydrocarbon tail, which decreases phospholipid mobility. This stiffening effect also reduces the water-soluble permeability of the bilayer but does not affect membrane fluidity.

All above lipids combine in a fashion to form lipid bilayer according but their position in lipid membrane are differential *i. e.* some of them are more toward the cytoplasm and some are more towards the outer sides. Some lipids are associated with proteins are known as **lipoprotein** and those are associated with carbohydrates are known are **glycolipids**.

2. Proteins

While membrane lipids form the basic structure of the lipid bilayer, the functions of the membrane are depending on the proteins it have. Cell adhesion, energy transduction, signaling, cell recognition and transport are just some of the important biological processes carried out by membrane proteins. There are three ways proteins can associate with the plasma membrane: (**Figure 1.2**)

1. **Intrinsic / Integral** membrane proteins that are embedded in the hydrophobic region of the lipid bilayer. Experimentally, these proteins can only be isolated by physically disrupting the membrane with detergent or other non-polar solvent. **Transmembrane** that span across the membrane once (single-pass), or multiple times (multi-pass). These transmembrane protein often bind to carbohydrates to form glycoprotein e. g. A, B and O blood Group protein on Red blood Cells. Some lipoproteins are also associated with transmembrane proteins. These span the membrane, typically in an α-helix conformation and can span the membrane multiple times. Some integral membrane proteins use β-barrels to cross the membrane. These structures are typically large and form water filled channels.
2. **Extrinsic or Peripheral membrane proteins** that associate weakly with the hydrophilic surfaces of the lipid bilayer or intrinsic membrane proteins. They form weak hydrophobic, electrostatic or non-covalent bonds, but do not embed with the hydrophobic core of the membrane. These proteins can be dissociated from the membrane without disrupting it through application of polar reagents or high pH solutions. Extrinsic membrane proteins may interact with the inner or outer leaflet.

3. Carbohydrate

Carbohydrates form specialized sites on the cell surface that allow cells to recognize each other. This recognition behavior is very important to cells, as it allows the immune system to differentiate between body cells (called “self”) and foreign cells or tissues (called “non-self”).

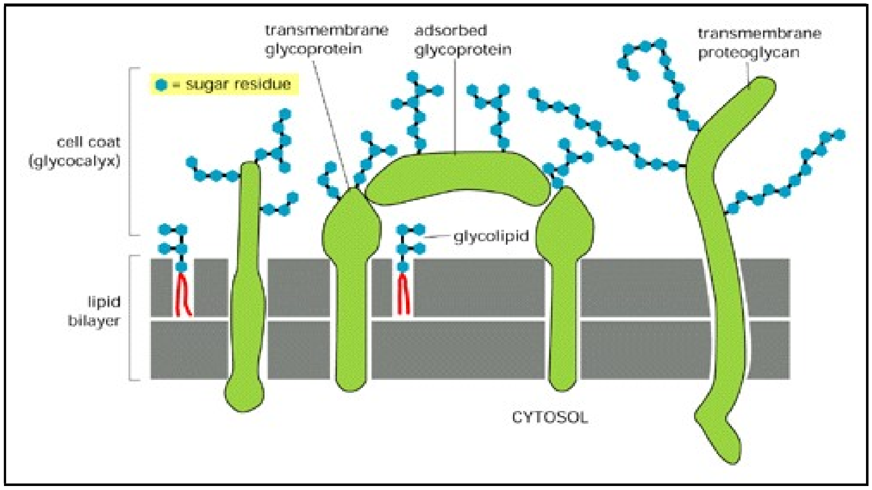


Figure 1.2 Simplified diagram of the cell coat (glycocalyx). The cell coat is made up of the oligosaccharide side chains of glycolipids and integral membrane glycoproteins and the polysaccharide chains on integral membrane proteoglycans. In addition, adsorbed glycoproteins and adsorbed proteoglycans (not shown) contribute to the glycocalyx in many cells. Note that all of the carbohydrate is on the noncytoplasmic surface of the membrane.

Source – Albert et al.

Similar types of **glycoproteins** and **glycolipids** are found on the surfaces of viruses and may change frequently, preventing immune cells from recognizing and attacking them. These carbohydrates on the exterior surface of the cell—the carbohydrate components of both glycoproteins and glycolipids—are collectively referred to as the glycocalyx (meaning “sugar coating”)The glycocalyx is highly hydrophilic and attracts large amounts of water to the surface of the cell. This aids in the interaction of the cell with its watery environment and in the cell’s ability to obtain substances dissolved in the water. Figure 1.2The most common oligosaccharides of cell membrane of mammalian erythrocytes and liver cells are hexose, hexosamine, fucose and sialic acid. Salic acid is sensitive to neuraminidase and is attached to proteins by N-acetylgalactosamine on the outer surface of the membrane.

Function of the Plasma Membrane

Plasma membrane control and performs all the living functions that are required for cell and organism survival. These are given below-

1. Plasma membrane controls movement of molecules in and out of the cell and functions in cell-cell signaling and cell adhesion.
2. Mitochondria, which are surrounded by a double membrane, generate ATP by oxidation of glucose and fatty acids
3. Lysosomes, which have an acidic lumen, degrade material internalized by the cell and worn-out cellular membranes and organelles.
4. Nuclear envelope, a double membrane, encloses the contents of the nucleus; the outer nuclear membrane is continuous with the rough ER.
5. Nucleolus is a nuclear subcompartment where most of the cell's rRNA is synthesized.
6. Nucleus is filled with chromatin composed of DNA and proteins; in dividing cells is site of mRNA and tRNA synthesis.
7. Smooth endoplasmic reticulum (ER) synthesizes lipids and detoxifies certain hydrophobic compounds.
8. Rough endoplasmic reticulum (ER) functions in the synthesis, processing, and sorting of secreted proteins, lysosomal proteins, and certain membrane.
9. Golgi complex processes and sorts secreted proteins, lysosomal proteins, and membrane proteins synthesized on the rough ER.
10. Secretory vesicles store secreted proteins and fuse with the plasma membrane to release their contents.
11. Peroxisomes detoxify various molecules and also break down fatty acids to produce acetyl groups for biosynthesis.
12. Cytoskeletal fibers form networks and bundles that support cellular membranes, help organize organelles, and participate in cell movement.
13. Microvilli increase surface area for absorption of nutrients from surrounding medium.
14. Cell wall, composed largely of cellulose, helps maintain the cell's shape and provides protection against mechanical stress.
15. Vacuole stores water, ions, and nutrients, degrades macromolecules, and functions in cell elongation during growth.
16. Chloroplasts, which carry out photosynthesis, are surrounded by a double membrane and contain a network of internal membrane-bounded sacs.

Structural Models of the Plasma Membrane

Before the advancement of microscopy, the plasma membrane was not structurally very clear to the scientists. Therefore, the different forms of hypothetical structure of the plasma membrane were deduced from the findings of above compositional ratios of lipids, proteins and carbohydrates by scientists from time to time. These hypothetical structures are known as Models of plasma membrane that were tried to satisfy its physical and biological properties on the basis of its chemical composition. Among them the top three historical models of Plasma Membrane are –

1. **Lipid and Lipid Bilayer Models by Overton (1902) Gorter and Grendel (1926).**

2. **Unit Membrane Model (Protein-Lipid Bilayer-Protein) Davson Daniell and Robertson.**

3. **Fluid Mosaic Model by Singer and Nicholson (1912)**

The most acceptable of the above models is the Fluid Mosaic Model that is most satisfactory up to biological and physical processes even today by scientists.

Fluid Mosaic Model by Singer and Nicholson (1912)

It was proposed by Singer and Nicholson (1912). This model explains that there are two lipids (Phospholipids) of fats layers in which the proteins and carbohydrates are embedded in mosaic patterns (here and there). The lipid and integrated proteins are disposed in a sort of mosaic pattern and all the biological membranes have a quasi-fluid structure as mentioned above where both lipid and protein components are able to perform transitional movement within lipid bilayer. The main fabric of the membrane is composed of amphiphilic or dual-loving, phospholipid molecules. The hydrophilic or water-loving areas of these molecules are in contact with the aqueous fluid outside the cell. Hydrophobic, or water-hating molecules, tend to be non- polar inside the cell. Some protein molecules are embedded into the bilayers of lipids that are known as Integral proteins (some specialized types are called **integrins**). Those proteins associated with lipids are known as lipoprotein and found on the outside of the cell are extrinsic proteins and in the cells are intrinsic proteins those are the cell adhesion molecules Carbohydrates are the third major component of plasma membranes They are always found on the exterior surface of cells and are bound either to proteins (forming glycoproteins) or to lipids (forming glycolipids). These carbohydrate chains may consist of 2–60 monosaccharide units and can be either straight or branched along with peripheral proteins. (**Figure 1.3**).

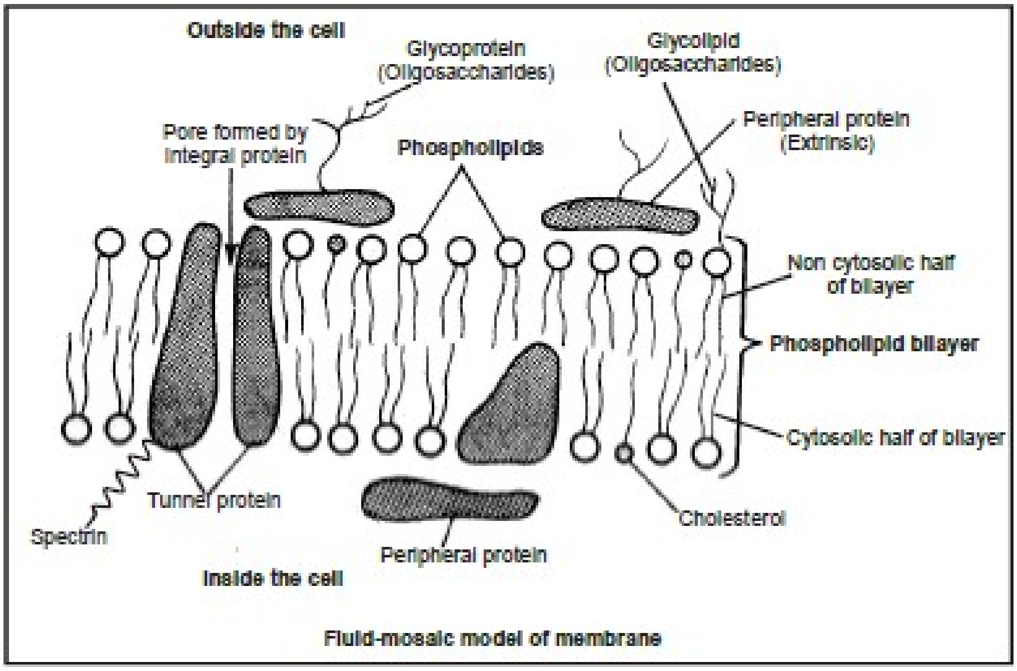


Figure 1.3 Diagrammatic representation of Fluid Mosaic Model

Chapter 2

Cell-cell interaction: cell adhesion molecules, cellular junctions

The cells in multicellular organisms are always jointed with each other or surrounded by matrices. The joining points of two cellular junctions and the molecules that help in joining are known as cell adhesion molecules. They interact with each other through their joining and work coordinately in groups. **If cell - cell interaction fails then an impairment of function occurs that ultimately converts into a disease.**

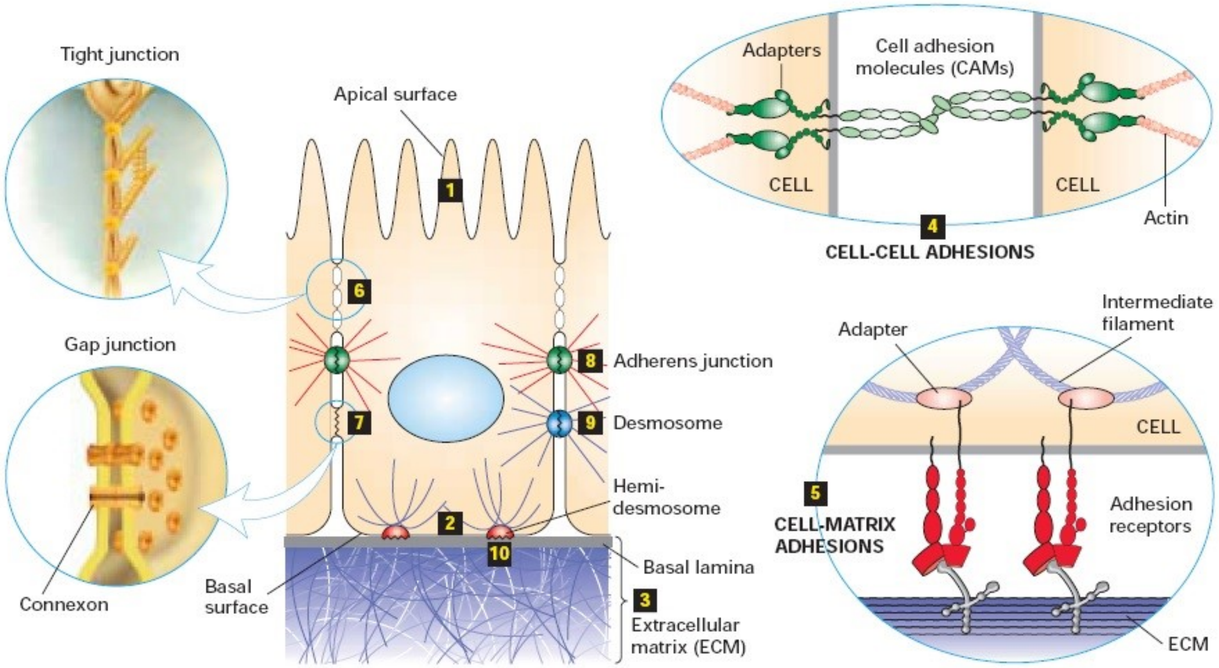


Figure 2 **Schematic overview of major adhesive interactions that bind cells to each other and to the extracellular matrix.** Schematic cutaway drawing of a typical epithelial tissue, such as the intestines. The apical (upper) surface of these cells is packed with fingerlike microvilli **1** that project into the intestinal lumen, and the basal (bottom) surface **2** rests on extracellular matrix (ECM). The ECM associated with epithelial cells is usually organized into various interconnected layers (e.g., the basal lamina, connecting fibers, connective tissue), in which large, interdigitating ECM macromolecules bind to one another and to the cells **3**. Cell-adhesion molecules (CAMs) bind to CAMs on other cells, mediating cell–cell adhesions **4**, and adhesion receptors bind to various components of the ECM, mediating cell–matrix adhesions **5**. Both types of cell-surface adhesion molecules are usually integral membrane proteins whose cytosolic domains often bind to multiple intracellular adapter proteins. These adapters, directly or indirectly, link the CAM to the cytoskeleton (actin or intermediate filaments) and to intracellular signaling pathways. As a consequence, information can be transferred by CAMs and the macromolecules to which they bind from the cell exterior into the intracellular environment, and vice versa. In some cases, a complex aggregate of CAMs, adapters, and associated proteins is assembled. Specific localized aggregates of CAMs or adhesion receptors form various types of cell junctions that play important roles in holding tissues together and facilitating communication between cells and their environment. Tight junctions **6**, lying just under the microvilli, prevent the diffusion of many substances through the extracellular spaces between the cells. Gap junctions **7** allow the movement through connexon channels of small molecules and ions between the cytosols of adjacent cells. The remaining three types of junctions, adherens junctions **8**, spot desmosomes **9**, and hemidesmosomes **10**, link the cytoskeleton of a cell to other cells or the ECM. [See V. Vasioukhin and E. Fuchs, 2001, *Curr. Opin. Cell Biol.* **13**:76.] ***Source - Lodish et al.***

Types of Cell - Cell interactions

When the cells interacts by close contact of **plasma membrane is** known as **Direct interaction** and when direct interaction mediated by intercellular space matrices is known as **Extracellular matrix interactions** (**3 of Figure 2**).

Direct interactions

These types of interactions are performed by the exchanges of big molecules that enter and exit the cell called endocytosis (entering inside the cell) and exocytosis (exiting outside the cell). For smaller particles like amino acids, water, ions and other solutes there are transported by direct contact between the cells called **Gap junctions**.

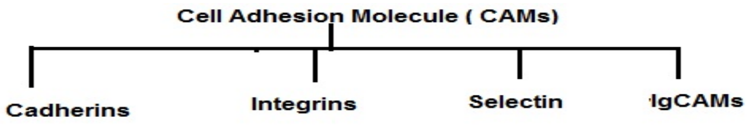
1. **Exocytosis** - by secreting various types of waste products and protein molecules (hormones and enzymes). that activate other cell types.
2. **Endocytosis** - bringing in the foods by Phagocytosis, water by Pinocytosis and response to others cells by receiving their massage molecules through Receptor-mediated endocytosis and Gap Junctions (7 of Figure 2 : special types of cell cell contacts that allow the exchange of molecules with specific directions). The best example of such interactions is the interactions of white blood cells to sites of tissue inflammation.

Extracellular matrix

Cellular interactions with the extracellular matrix (**5 of Figure 2**: ECM) are complex. Not only does the ECM provide structural support to cells and tissues, but it is also responsible for generating **cell signals** that are capable of affecting **cell proliferation** and **differentiation**, **cell migration**, and **cell adhesion**. The extracellular matrix serves as the scaffolding for tissues and organs throughout the body, playing an essential role in their structural and functional integrity. Its predominant components are the large, insoluble structural proteins collagen and elastin. Extracellular matrix molecules are a part of a finely regulated system of development, maintenance, and repair.

Cell Adhesion Molecules

Cell ***a***dhesion ***m***olecules (**4 of Figure 2**: CAMs) are a subset of cell surface proteins found in the plasma membrane that are helped in the binding of cells with other cells or with the extracellular matrix (ECM), in a process called cell adhesion i.e. CAMs help cells stick to each other and to their surroundings. These molecules play an integral role in generating force and movement and consequently ensuring that organs are able to execute their functions normally. In addition to serving as "**molecular glue**", CAMs play important roles in the cellular mechanisms of growth, contact inhibition, and apoptosis. Aberrant expression of CAMs may result in a wide range of pathologies, ranging from frostbite to cancer. There are four **Major Groups of *C*ell *A*dhesion *M*olecules** (**CAMs**)



One classification system involves the distinction between calcium-independent CAMs and calcium-dependent CAMs. **Integrins** and the **Ig-superfamily** CAMs do not depend on Ca^{2+} while cadherins and selectins depend on Ca^{2+}. In addition, integrins participate in cell–matrix interactions, while other CAM families participate in cell–cell interactions.

Cadherins

Cadherins are a group of proteins that help cells stick together. They are the main components of certain types of junctions between cells (4 of Figure 2). These connections help define how a cell will be integrated into a structure, like a layer of skin or an organ. Within the junctions, cadherin molecules on the cell surfaces hook onto each other, like a tiny piece of velcro. **There are about one hundred types of cadherins in vertebrates, and they fall into four groups.** Classical cadherins include **E-cadherin**, **N-cadherin**, **P-cadherin** and **N-cadherin 2**. They all have a similar structure, with five extracellular cadherin repeats, a transmembrane domain, and an intracellular domain (Figure 2.1).

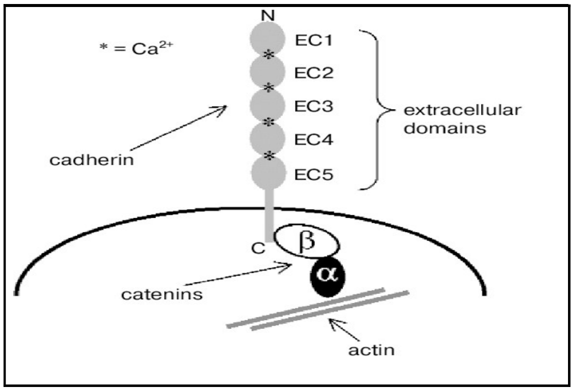


Figure 2.1- Molecular representation of a Catherin molecule.

Functions of Cadherins

1. Cell-to-cell adhesion mediated by cadherins plays an important role in tissue differentiation, holding the tissues together as they form during embryonic development.
2. Adhesion by classic cadherins is involved in some significant cellular signaling pathways, including **Wnt**, **Hedgehog**, **Ras**, and RhoGTPase signaling. This means cadherins have a critical role in many biological processes.
3. **Desmoglein and desmocollin are desmosomal cadherins**. They are important in forming a type of cellular junction called a **desmosome**.
4. **Protocadherins** are a large group of cadherin molecules present in a wide range of species that are thought to be related to an ancestral cadherin. They are highly variable, with a variety of functions in the nervous system, including neuronal differentiation and the formation of synapses.
5. Unconventional cadherins are a large group of cadherins that are not otherwise categorized into the previous three groups. They include **VE-cadherin**, **R-cadherin**, and many others.
6. In vertebrates, cadherins are responsible for holding most epithelial sheets together. This includes the linings of the small intestine or kidney tubules.
7. Cadherins' role in cancer **E-cadherin**, a member of the cadherin family, has a very important role in organizing the epithelium. Most cancers arise from epithelial tissue, and in those cancers, cell adhesion mediated by E-cadherin is lost at the same time that a tumor progresses toward malignancy.
8. Cell organization- Cadherins are also important in other aspects of cell organization, like the formation of boundaries, coordinated cell movements, and maintenance of structural and functional cell and tissue polarity. In addition to E-cadherin's role in the formation of epithelium, N-cadherin is important in neural tissue and muscle, R-cadherin is used in brain and bone tissue, P-cadherin is present in skin, and VE-cadherin is also significant in the epithelium.

Two types of cellular junctions rely on cadherins. Aherens junctions have a strip of cadherin molecules that connect the membranes of epithelial cells. The epithelium is a thin tissue that forms layers on hollow structures of the body, like the intestine. Desmosomes also rely on cadherins. A desmosome is a structure inside the membrane of a cell. It uses the cadherins, desmoglein and desmocollin to penetrate through the membrane and form an interlocking network that binds cells together.

Integrin - Its structure and functions

Integrins are proteins that function mechanically, by attaching the cell cytoskeleton to the extracellular matrix (ECM), and biochemically, by sensing whether adhesion has occurred. The integrin family of proteins consists of alpha and beta subtypes, which form transmembrane heterodimers. Integrins function as adhesion receptors for extracellular ligands and transduce biochemical signals into the cell, through downstream effector proteins. Remarkably, they function bidirectionally, meaning they can transmit information both outside-in and inside-out Each integrin heterodimer consists of an alpha (α) and a beta (β) subunit associated by noncovalent interactions forming an extracellular ligand-binding head, two multi-domain `legs’, two single-pass transmembrane helices and two short cytoplasmic tails. The α and β groups show no homology to each other,however, conserved regions are found among subtypes of both groups.

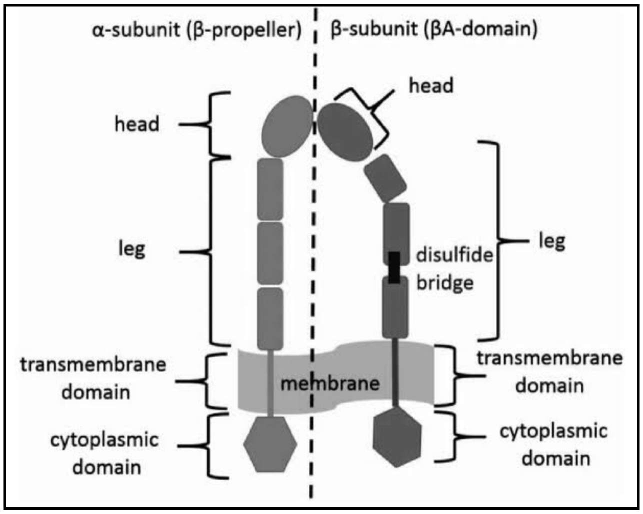


Figure 2.2 - Molecular representation of a Integrin molecule.

Immunoglobin (Ig) - superfamily (CAMs)

The **Ig** superfamily CAMs are calcium-independent transmembrane glycoproteins. Each **Ig** superfamily CAM has an extracellular domain, which contains several Ig-like intra-chain disulfide-bonded loops with conserved cysteine residues, a transmembrane domain, and an intracellular domain that interacts with the cytoskeleton. Typically, cell adhesion molecules bind integrins or other **Ig** superfamily CAMs. of the Ig superfamily include the intercellular adhesion molecules (**ICAMs**), vascular-cell adhesion molecule (**VCAM-1**), platelet-endothelial-cell adhesion molecule (PECAM-1), neural-cell adhesion molecule (NCAM). **Figure 2.3**

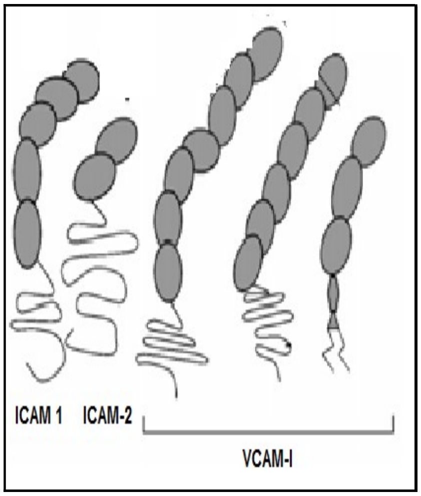


Figure 2.3 Molecular Diagrams of Ig CAMs

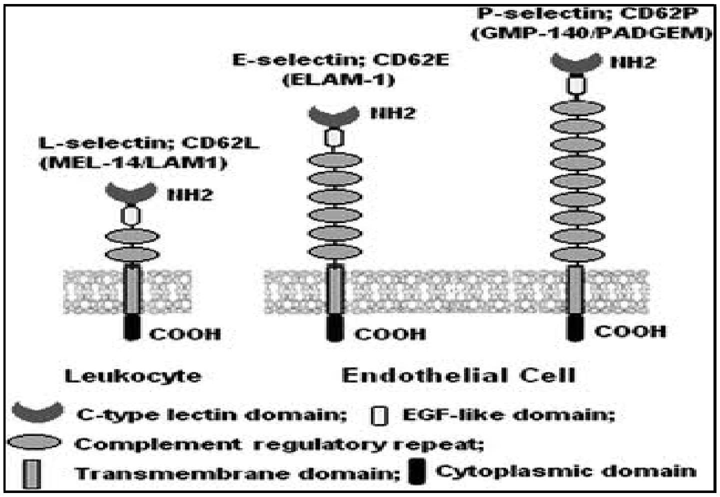


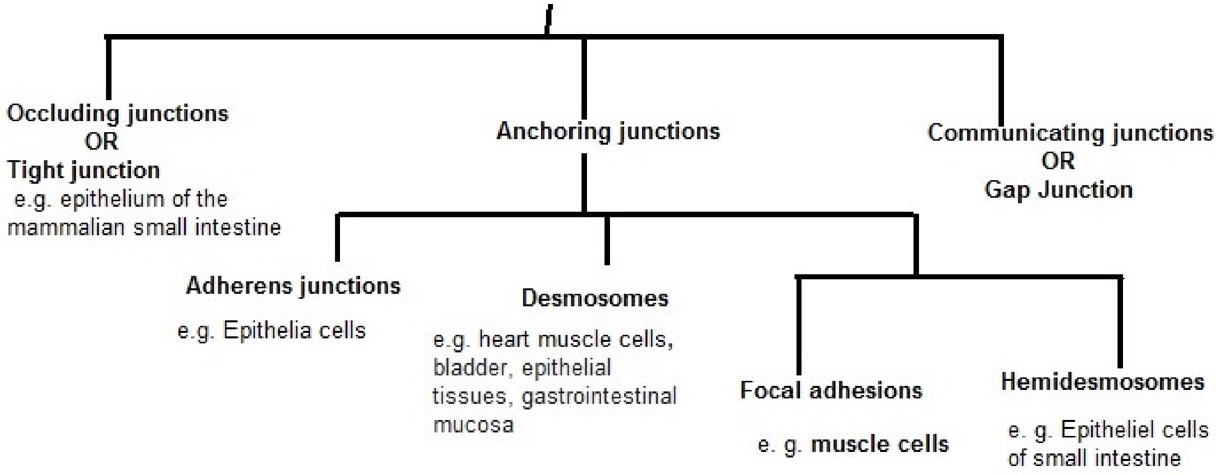
Figure 2.4 Molecular representation of various Selectin CAMs and their arrangement.

Selectin - Types and Functions

The selectins are a family of cell adhesion molecules (or CAMs). All selectins are single-chain **transmembrane glycoproteins** that share similar properties to C-type lectins due to a related amino terminus and calcium-dependent binding. Selectins bind to sugar moieties and so are considered to be a type of lectin, cell adhesion proteins that bind sugar polymers. Members of the selectin family, E-selectin (endothelial), L-selectin (leukocyte) and P-selectin (platelet), all of which bind to fucosylated carbohydrates In collaboration with other CAM families, selectins play important roles in leukocyte trafficking to the sites of inflammation. For example, the rolling of leukocytes along the endothelium is mediated by selectins, whereas the firm adhesion and transendothelial migration of leukocytes require interaction between the integrin family and Ig-CAMs such as ICAM-1 and VCAM-1.

Cellular Junctions

The plasma membranes of adjacent cells are usually separated by extracellular fluids that allow transport of nutrients and wastes to and from the bloodstream. In certain tissues, however, the membranes of adjacent cells may join and form a junction. Cell junctions can be classified into three functional groups:



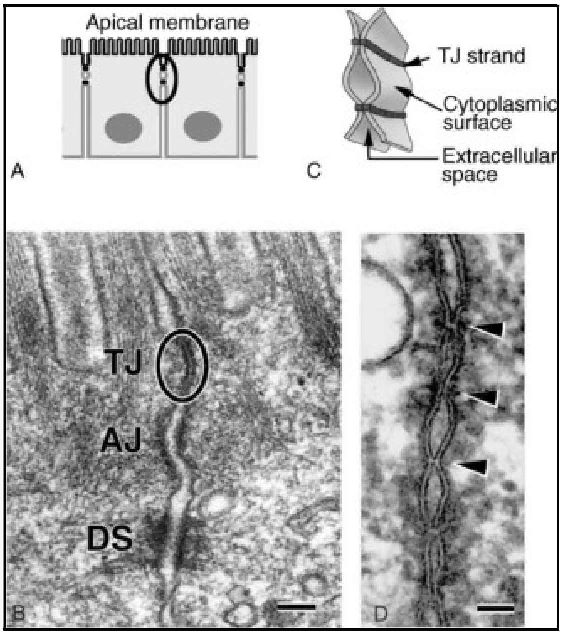
1. **Occluding junctions** seal cells together in an epithelium in a way that prevents even small molecules from leaking from one side of the sheet to the other. (**Tight junction**, **6 and 8 of Figure 2**)
2. **Anchoring junctions** mechanically attach cells (and their cytoskeletons) to their neighbors or to the extracellular matrix (**Hemi desmosome, 10 of Figure 2**)
3. **Communicating junctions** mediate the passage of chemical or electrical signals from one interacting cell to its partner (**Gap Junction, 7 of Figure 2**)

Occluding Junctions

All epithelia have at least one important function in common: they serve as selective permeability barriers, separating fluids on either side that have a different chemical composition. (**Tight junction**, **6 and 8 of Figure 2**). This function requires that the adjacent cells be sealed together by occluding junctions. **Tight junctions** (**Figure 2 .5**) have this barrier role in vertebrates, Example is the epithelium of the mammalian small intestine, or gut. Furthermore, the spaces between epithelial cells must be tightly sealed, so that the transported molecules cannot diffuse back into the gut lumen through these spaces

Figure 2.5

Structure of tight junctions. (A) Schematic drawing of simple epithelial cells. The junctional complex is located at the most apical part of lateral membranes (encircled). (B) Electron micrograph of the junctional complex in mouse intestinal epithelial cells. TJ, tight junction (encircled); AJ, adherens junction; DS, desmosome. (C) Schematic drawing of tight junctions. Individual tight junction strand within plasma membranes associates laterally with another strand in apposing membranes to form a paired strand. (D) Ultra-thin sectional view of tight junctions. At kissing points of TJs (arrowheads), the intercellular space is obliterated. Bars, 200 nm (b); 50 nm (d). Shoichiro Tsukita, Encyclopedia of Biological Chemistry, 2004.



Tight Junctions - Structure and Functions

First, they function as barriers to the diffusion of some membrane proteins (and lipids) between apical and basolateral domains of the plasma membrane. Each tight junction sealing strand is composed of a long row of transmembrane adhesion proteins embedded in each of the two interacting plasma membranes. The extracellular domains of these proteins join directly to one another to occlude the intercellular space (**Figure 2. 6**). The major transmembrane proteins in a tight junction are the **claudins**, which are essential for tight junction formation and function and differ in different tight junctions. A second major transmembrane in protein tight junctions is **occludin**, the function of which is uncertain. Claudins and occludins associate with intracellular peripheral membrane proteins called **ZO proteins** (a tight junction is also known as a **zonula occludens**), which anchor the strands to the actin cytoskeleton. In addition to claudins, occludins, and ZO proteins, several other proteins can be found associated with tight junctions.

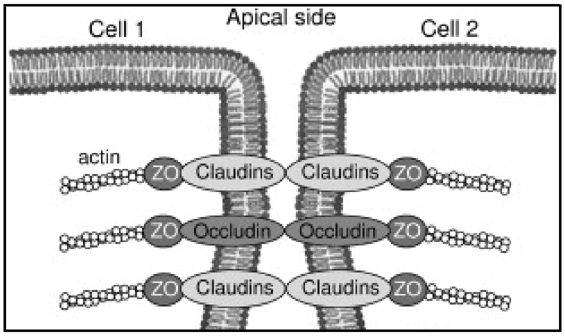


Figure 2.6 Diagram of Molecular arrangement in a tight junctions.

These include some that regulate epithelial cell polarity and others that help guide the delivery of components to the appropriate domain of the plasma membrane. Thus, the tight junction may serve as a regulatory center to help in coordinating multiple cell processes **(Figure 2. 6)**.

In invertebrates, septate junctions are the main occluding junction. More regular in structure than a tight junction, they likewise form a continuous band around each epithelial cell. But their morphology is distinct because the interacting plasma membranes are joined by proteins that are arranged in parallel rows with a regular periodicity. A protein called Discs-large, which is required for the formation of septate junctions in Drosophila, is structurally related to the ZO proteins found in vertebrate tight junctions.

Anchoring Junctions

These (**4, 5, 8 and 10 of Figure 2**) Connect the Cytoskeleton of a Cell either to the Cytoskeleton of its Neighbors or to the Extracellular Matrix. The lipid bilayer is flimsy and cannot by itself transmit large forces from cell to cell or from cell to extracellular matrix. Anchoring junctions solve the problem by forming a strong membrane-spanning structure that is tethered inside the cell to the tension-bearing filaments of the cytoskeleton. Anchoring junctions are widely distributed in animal tissues and are most abundant in tissues that are subjected to severe mechanical **stress, such as heart, muscle, and epidermis**. They are composed of two main classes of proteins. Intracellular anchor proteins form a distinct plaque on the cytoplasmic face of the plasma membrane and connect the junctional complex to either actin filaments or intermediate filaments. Transmembrane adhesion proteins have a cytoplasmic tail that binds to one or more intracellular anchor proteins and an extracellular domain that interacts with either the extracellular matrix or the extracellular domains of specific transmembrane adhesion proteins on another cell. In addition to anchor proteins and adhesion proteins, many anchoring junctions contain intracellular signaling proteins that enable the junctions to signal to the cell interior. Anchoring junctions occur in two functionally different forms:

1. **Adherens junctions**
2. **Desmosomes.**
3. **Focal adhesions and hemidesmosomes**

On the intracellular side of the membrane, adherens junctions and focal adhesions serve as connection sites for actin filaments, while desmosomes and hemidesmosomes serve as connection sites for intermediate filaments.

Adherens Junctions

Adherens Junctions (**4, 5, 8 and 9 of Figure 2**) hold cells together and are formed by transmembrane adhesion proteins that belong to the **cadherin** family. These Connect Bundles of Actin Filaments from Cell to Cell. Adherens junctions occur in various forms. In many non epithelial tissues, they take the form of small punctate or streak like attachments that indirectly connect the cortical actin filaments beneath the plasma membranes of two interacting cells. But the prototypical examples of adherens junctions occur in **epithelia**, where they often form a continuous adhesion belt (or zonula adherens) just below the tight junctions (**Figure 2.5, AJ**), encircling each of the interacting cells in the sheet. The adhesion belts are directly opposed in adjacent epithelial cells, with the interacting plasma membranes held together by the cadherins that serve here as transmembrane adhesion proteins.

Within each cell, a contractile bundle of actin filaments lies adjacent to the adhesion belt, oriented parallel to the plasma membrane. The actin is attached to this membrane through a set of intracellular anchor proteins, including catenins, vinculin, and α-actinin. The actin bundles are thus linked, via the cadherins and anchor proteins, into an extensive transcellular network (**Figure 2.7**).

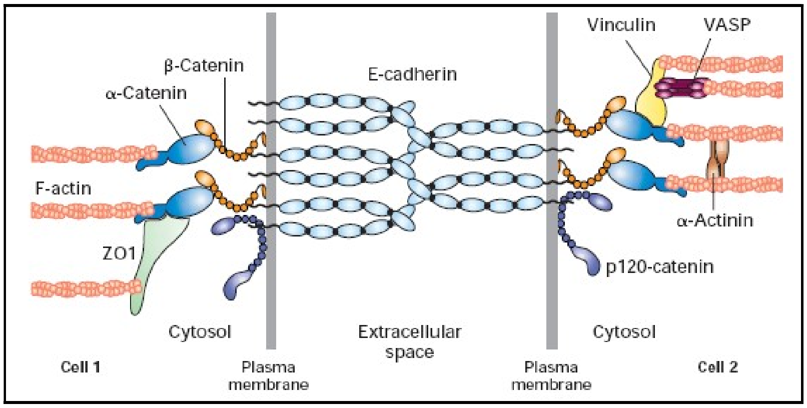


FIGURE 2.7 Protein constitutents of typical adherens junctions. *Source Lodish et al.*

Desmosomes

Desmosomes (**8 of Figure 2, 2.5 DS**) are button like points of intercellular contact that rivet cells together and **Connect Intermediate Filaments from Cell to Cell** (**Figure 2.8**). Inside the cell, they serve as anchoring sites for ropelike intermediate filaments, which form a structural framework of great tensile strength. Through desmosomes, the intermediate filaments of adjacent cells are linked into a net that extends throughout the many cells of a tissue.

The particular type of intermediate filaments attached to the desmosomes depends on the cell type: they are **keratin filaments** in most epithelial cells, for example, and **desmin filaments** in heart muscle cells**,** bladder tissues, epithelial tissues, and gastrointestinal mucosa. (**Figure 2.8**). These antibodies bind to and disrupt the desmosomes that hold their skin epithelial cells (keratinocytes) together. This results in a severe blistering of the skin, with leakage of body fluids into the loosened epithelium. The junction has a dense cytoplasmic plaque composed of a complex of intracellular anchor proteins (**plakoglobin and desmoplakin**) that are responsible for connecting the cytoskeleton to the transmembrane adhesion proteins. These adhesion proteins (**desmoglein** and **desmocollin**), like those at an adherens junction, belong to the cadherin family.

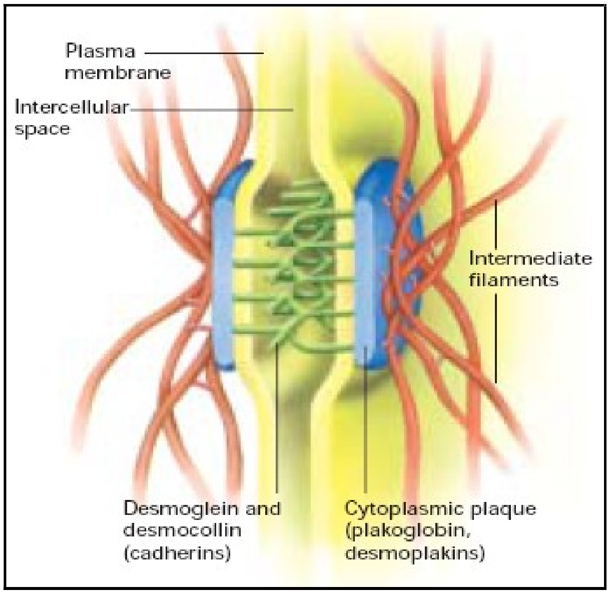

Plasma membrane
Intercellular space
Intermediate filaments
Desmoglein and desmocollin (cadherins)
Cytoplasmic plaque (plakoglobin, desmoplakins)

FIGURE 2.8 Desmosomes. Schematic model showing components of a desmosome between epithelial cells and attachments to the sides of keratin intermediate filaments, which crisscross the interior of cells. The transmembrane CAMs, desmoglein and desmocollin, belong to the cadherin family. *Source Lodish et al.*

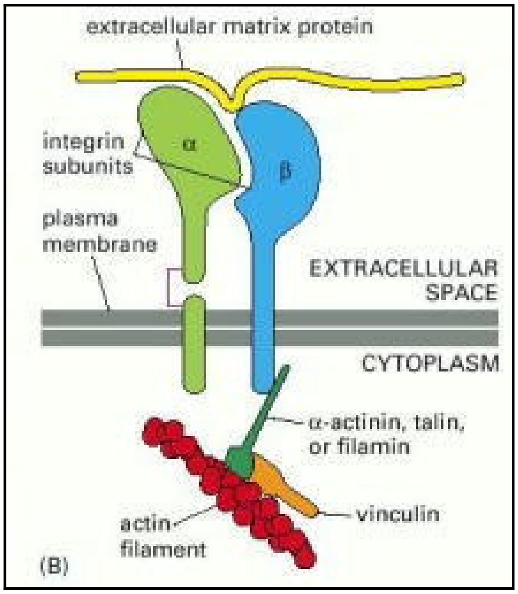


Figure 2.9 Some of the proteins that form focal adhesions. The transmembrane adhesion protein is an integrin heterodimer, composed of an α and a β subunit. Its extracellular domains bind to components of the extracellular matrix, while the cytoplasmic tail of the β subunit binds indirectly to actin filaments via several intracellular anchor proteins. *Source Alberts et al.*

Anchoring Junctions

These adhesion proteins (**desmoglein** and **desmocollin**), like those at an adherens junction, belong to the cadherin family. They interact through their extracellular domains to hold the adjacent plasma membranes together. The importance of desmosome junctions is demonstrated by some forms of the potentially fatal skin disease pemphigus. Affected individuals make antibodies against one of their own desmosomal cadherin proteins.

These junctions bind cells to the extracellular matrix and are formed by transmembrane adhesion proteins of the integrin family (**5** of **FIGURE 2**)**.** These are formed by **Integrins** Bind Cells to the Extracellular Matrix. There are of two types: Focal Adhesions and Hemidesmosomes.

Focal Adhesions

Some anchoring junctions bind cells to the extracellular matrix rather than to other cells. The transmembrane adhesion proteins in these cell-matrix junctions are integrins—a large family of proteins distinct from the cadherins. Focal adhesions enable cells to get a hold on the extracellular matrix through integrins that link intracellularly to actin filaments. In this way, **muscle cells**, for example, **attach to their tendons at the myotendinous junction.** Likewise, when cultured fibroblasts migrate on an artificial substratum coated with extracellular matrix molecules, they also grip the substratum at focal adhesions, where bundles of actin filaments terminate. At all such adhesions, the extracellular domains of transmembrane integrin proteins bind to a protein component of the extracellular matrix, while their intracellular domains bind indirectly to bundles of actin filaments via the intracellular anchor proteins talin, α-actinin, filamin, and vinculin **(Figure 2.9)**.

Hemidesmosomes

Hemidesmosomes, or half-desmosomes **(10 of Figure 2 and Figure 2. 10)**, resemble desmosomes morphologically and in connecting to intermediate filaments, and, like desmosomes, they act as rivets to distribute tensile or shearing forces through an epithelium. Instead of joining adjacent epithelial cells, however, hemidesmosomes connect the **basal** surface of an epithelial cell to the underlying basal lamina (**Figure 2. 10 A**). The extracellular domains of the integrins that mediate the adhesion bind to a **laminin protein** in the basal lamina, while an intracellular **domain** binds via an anchor protein **(plectin) to keratin** intermediate filaments. Whereas the keratin filaments associated with desmosomes make lateral attachments to the desmosomal plaques (**Figure 2. 10B**), many keratin filaments associated with hemidesmosomes have their ends buried in the plaque (**Figure 2. 10 B).**

NOTE-

Although the terminology for the various anchoring junctions can be confusing, the molecular principles (for vertebrates, at least) are relatively simple (**Table 2**). Integrins in the plasma membrane anchor a cell to extracellular matrix molecules; cadherin family members in the plasma membrane anchor it to the plasma membrane of an adjacent cell. In both cases, there is an intracellular coupling to cytoskeletal filaments, either actin filaments or intermediate filaments, depending on the types of intracellular anchor proteins involved.

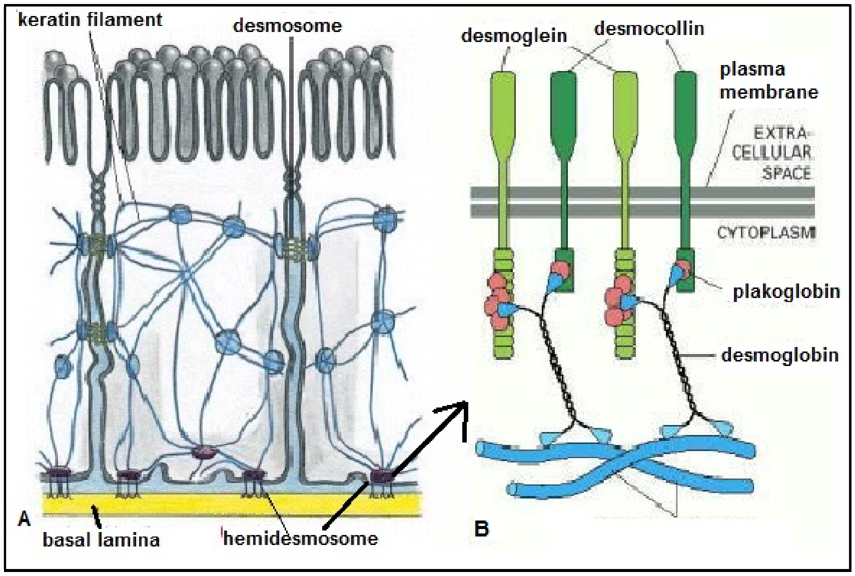


Figure 2. 10 A. The distribution of desmosomes and hemidesmosomes in epithelial cells of the small intestine. The keratin intermediate filament networks of adjacent cells are indirectly connected to one another through desmosomes and to the basal lamina through hemidesmosomes.
B. Some of the molecular components of a desmosome. Desmoglein and desmocollin are members of the cadherin family of adhesion proteins. Their cytoplasmic tails bind plakoglobin (γ-catenin), which in turn binds to desmoplakin. Desmoplakin also binds to the sides of intermediate filaments, thereby tying the desmosome to these filaments. *Source – Albarts et al.*

Table 2 Anchoring Junctions and their associated proteins. *Source- Alberts et al.*

JUNCTION	TRANSMEMBRANE ADHESION PROTEIN	EXTRACELLULAR LIGAND	INTRACELLULAR CYTOSKELETAL ATTACHMENT	INTRACELLULAR ANCHOR PROTEINS
Cell-Cell				
Adherens junction	cadherin (E-cadherin)	cadherin in neighboring cell	actin filaments	α- and β-catenins, vinculin, α-actinin, plakoglobin (γ-catenin)
Desmosome	cadherin (desmoglein, desmocollin)	desmogleins and desmocollins in neighboring cell	intermediate filaments	desmoplakins, plakoglobin (γ-catenin)
Cell-Matrix				
Focal adhesion	integrin	extracellular matrix proteins	actin filaments	talin, vinculin, α-actinin, filamin
Hemidesmosome	integrin $\alpha_6\beta_4$, BP180	extracellular matrix proteins	intermediate filaments	plectin, BP230

Gap Junctions

Gap Junctions **(7 of Figure 2 and Figure 2.11)** allows Molecules to pass directly from cell to cell. Most cells in animal tissues are in communication with their neighbors via gap junctions. Except few skeletal muscle cells and blood cells, Each gap junction appears in conventional electron micrographs as a patch where the membranes of two adjacent cells are separated by a uniform narrow gap of about 2–4 nm. The gap is spanned by channel-forming proteins *(connexins)*. The channels they form *(connexons)* allow inorganic ions and other small water-soluble molecules to pass directly from the cytoplasm of one cell to the cytoplasm of the other, thereby coupling the cells both electrically and metabolically **(Figure 2.11). Connexins** are four-pass transmembrane proteins, six of which assemble to form a channel, a **connexon**. When the connexons in the plasma membranes of two cells in contact are aligned, they form a continuous aqueous channel that connects the two cell interiors (**Figure 2.12**). The connexons hold the interacting plasma membranes at a fixed distance apart—hence the gap.

Dye-injection experiments suggest a maximal functional pore size for the connecting channels of about 1.5 nm, implying that coupled cells share their small molecules (such as inorganic ions, sugars, amino acids, nucleotides, vitamins, and the intracellular mediators cyclic AMP and inositol trisphosphate) but not their macromolecules (proteins, nucleic acids, and polysaccharides) (**Figure 2.12**). Gap junctions in different tissues can have different properties. The permeability of their individual channels can vary, reflecting differences in the connexins that form the junctions. In humans, for instance, there are 14 distinct connexins.

Functions of Gap Junctions

Some nerve cells, are electrically coupled by gap junction, allowing action potentials to spread rapidly from cell to cell, without the delay that occurs at chemical synapses.

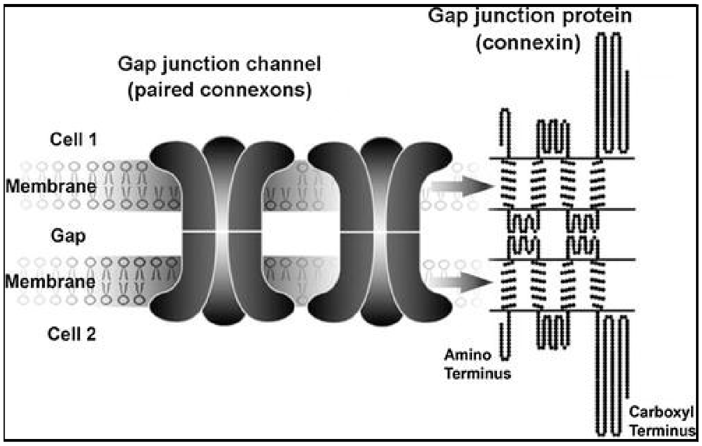

Gap junction protein (connexin)
Gap junction channel (paired connexons)
Cell 1
Membrane
Gap
Membrane
Cell 2
Amino Terminus
Carboxyl Terminus

Figure 2.11 Diagrammatic and Molecular representation of a Gap junction between two cells.

It also helps to synchronize the contractions of both heart muscle cells and the smooth muscle cells responsible for the peristaltic movements of the intestine. Gap junctions also coordinate the functions of cells in tissues by passing molecules such as hormones and ions.

1. In the liver, for example, the release of noradrenaline from sympathetic nerve endings in response to a fall in blood glucose levels stimulates hepatocytes to increase glycogen breakdown and release glucose into the blood. Not all the hepatocytes are innervated by sympathetic nerves, however. By means of the gap junctions that connect hepatocytes, the signal is transmitted from the innervated hepatocytes to the noninnervated ones.
2. The normal development of ovarian follicles also depends on gap-junction-mediated communication—in this case, between the oocyte and the surrounding granulosa cells.
3. Cell coupling via gap junctions also seems to be important in embryogenesis. In early vertebrate embryos, beginning with the late eight-cell stage in mouse embryos, most cells are electrically coupled to one another.

As specific groups of cells in the embryo develop their distinct identities and begin to differentiate, they commonly uncouple from surrounding tissue.

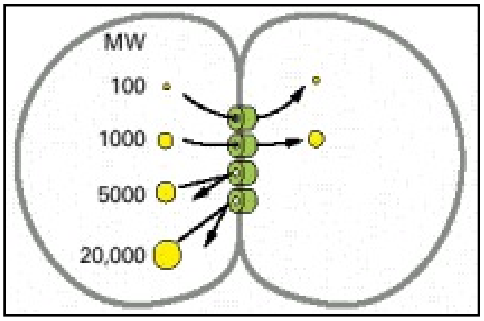


Figure 2.12 Determining the size of a gap-junction channel. When fluorescent molecules of various sizes are injected into one of two cells coupled by gap junctions, molecules with a mass of less than about 1000 daltons can pass into the other cell, but larger molecules cannot. *Source- Alberts at al.*

Plasmodesmata

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In Plants, Plasmodesmata perform many of the same functions as Gap junctions. Plant cells are firmly fixed by cellulose that is its basic component of cell wall. Thus, plant cells have only one class of intercellular junctions, **plasmodesmata** (singular, plasmodesma). Like gap junctions, they directly connect the cytoplasms of adjacent cells. Every living cell in a higher plant is connected to its living neighbors by these structures, which form fine cytoplasmic channels through the intervening cell walls. As shown in **Figure 2.13 A**, the plasma membrane of one cell is continuous with that of its neighbor at each plasmodesma, and the cytoplasm of the two cells is connected by a roughly cylindrical channel with a diameter of 20–40 nm. Thus, the cells of a plant can be viewed as forming a syncytium, in which many cell nuclei share a common cytoplasm.

Compositions of Plasmodesmata

Running through the center of the channel in most plasmodesmata is a narrower cylindrical structure, the *desmotubule,* which is continuous with elements of the smooth endoplasmic reticulum in each of the connected cells (**Figures 19-20B**). Between the outside of the desmotubule and the inner face of the cylindrical channel formed by plasma membrane is an annulus of cytosol through which small molecules can pass from cell to cell. As each new cell wall is assembled during the cytokinesis phase of cell division, plasmadesmata are created within it. They form around elements of smooth ER that become trapped across the developing cell plate

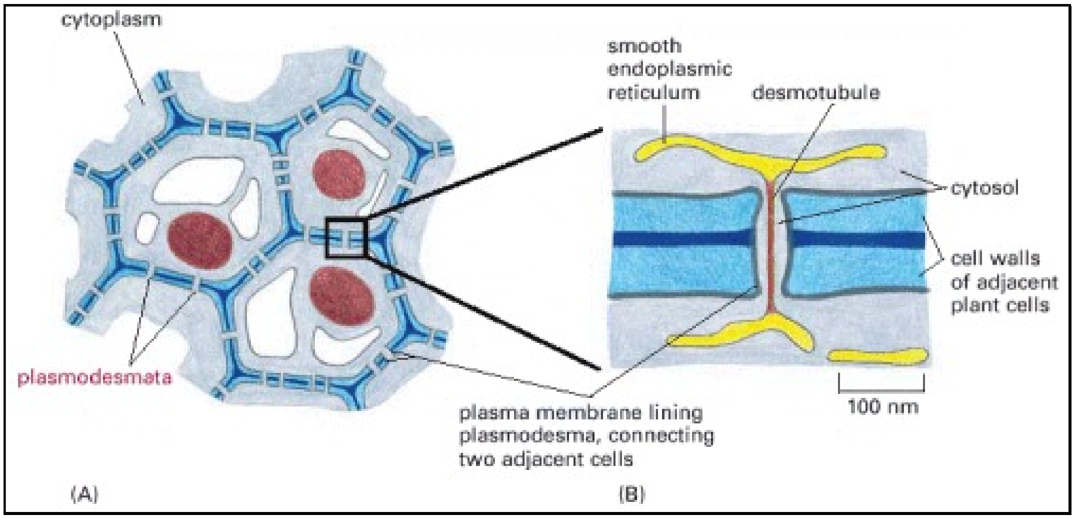
cytoplasm
plasmodesmata
smooth endoplasmic reticulum
desmotubule
cytosol
cell walls of adjacent plant cells
100 nm
plasma membrane lining plasmodesma, connecting two adjacent cells
(A)
(B)

Figure 2.13 (A) The cytoplasmic channels of plasmodesmata pierce the plant cell wall and connect all cells in a plant together. (B) Each plasmodesma is lined with plasma membrane that is common to two connected cells. It usually also contains a fine tubular structure, the desmotubule, derived from smooth endoplasmic reticulum.

Chapter 3

Endomembrane System

The endomembrane system is composed of **Endoplasmic Reticulum**, **Golgi bodies**, **Lysosomes**, **Endosomes** and **Secretory Vesicles**, **nuclear and plasma membrane**. These cell organelles are also known as **Cells' compartments.** The different types of proteins are synthesised freely in the cytoplasm with the help of Ribosomes or that are attached to the surface of Endoplasmic reticulum. The main function of endoplasmic reticulum is to transport the synthesized newly nascent protein molecules to different organelles of the cell. The newly synthesised proteins of cytoplasm are transported to other cell organelles by broadly three ways –

1. First way is direct transfers of proteins and macromolecules from nucleus to cytoplasm *vis-a-vis* through **gated transport**.
2. Second way is cytoplasm to Endoplasmic reticulum, mitochondria and peroxisome through **trans-membrane transport**.
3. Third way is transfer from ER to Golgi bodies and then to various organelles such as plasma membrane, lysosomes, endosomes, secretory vesicles through vascular transport.

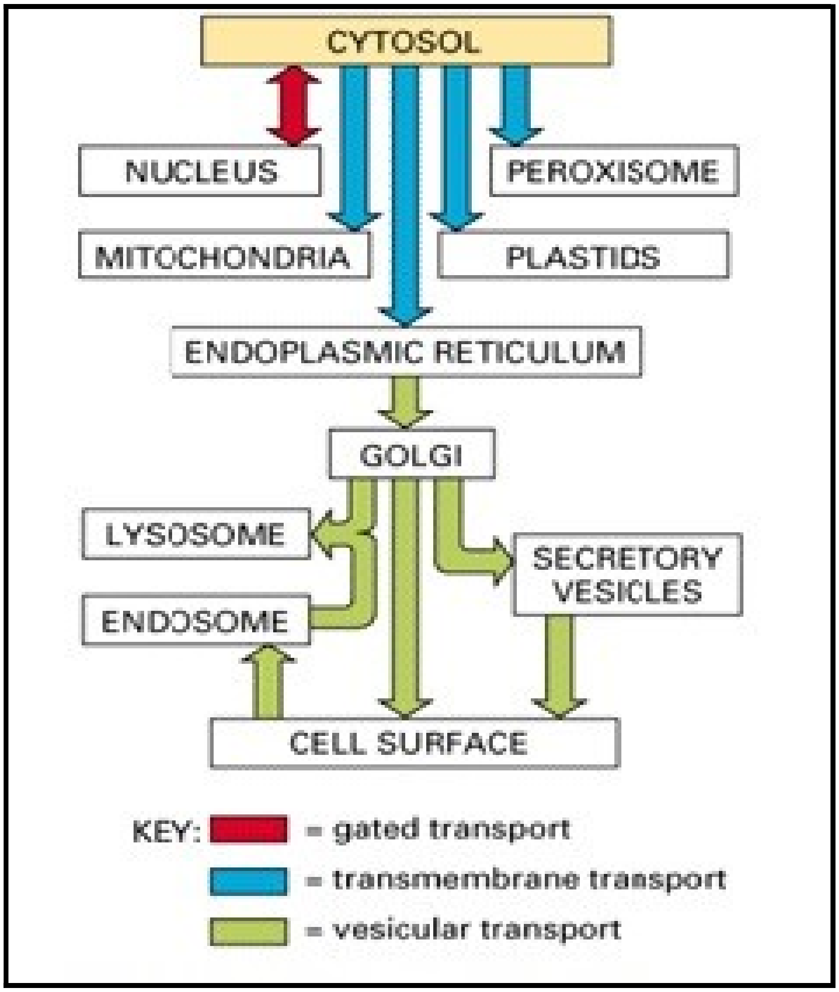

Figure 3.1 Overview of Proteins transport pathways various cell organelles.
*Source Alberts et al***.**

The Concept of Protein Shorting

At each intermediate cell organelles (at First, Second and Third step) a decision is made as to whether the protein is to be retained or transported further. This mechanism of decision to retain or transport the newly synthesised protein is **similar to shorting of proteins**. Each of the three modes of protein transfer is usually selectively guided by sorting signals in the transported protein that are recognized by complementary receptor proteins in the target organelle. If a large protein is to be imported into the nucleus, for example, it must possess a sorting signal that is recognized by receptor proteins associated with the nuclear pore complex. If a protein is to be transferred directly across a membrane, it must possess a sorting signal that is recognized by the translocator in the membrane to be crossed. Likewise, if a protein is to be incorporated into certain types of transport vesicles or to be retained in certain organelles, its sorting signal must be recognized by a complementary receptor in the appropriate membrane. The signals that direct a given protein's movement through the organelles, and thereby determine its eventual location of other organelles in the cell, are contained in its amino acid sequence. These signals are amino acids sequences that are synthesised during its translation when new proteins are formed. Further they are modified or sorted if required for the next step of transport.

Protein Sorting by Signal Peptides and Signal Patches

These signals of amino acid sequences direct the specific proteins to the Correct Cellular address of cell organelles. There are at least two types of sorting signals on proteins. One type resides in a continuous stretch of amino acid sequence, typically 15 to 60 residues long. This signal peptide is often (but not always) removed from the finished protein by a specialized signal peptidase once the sorting process has been completed. The other type consists of a specific three-dimensional arrangement of atoms on the protein's surface that forms when the protein folds up. The amino acid residues that comprise this signal patch can be distant from one another in the linear amino acid sequence, and they generally remain in the finished protein (Figure 12-8). Signal peptides are used to direct proteins from the cytosol into the ER, mitochondria, chloroplasts, peroxisomes, and nucleus, and they are also used to retain soluble proteins in the ER. **Signal patches** identify certain enzymes that are to be marked with specific sugar residues that then direct them from the Golgi apparatus into lysosomes; signal patches are also used in other sorting steps that have been less well characterized.

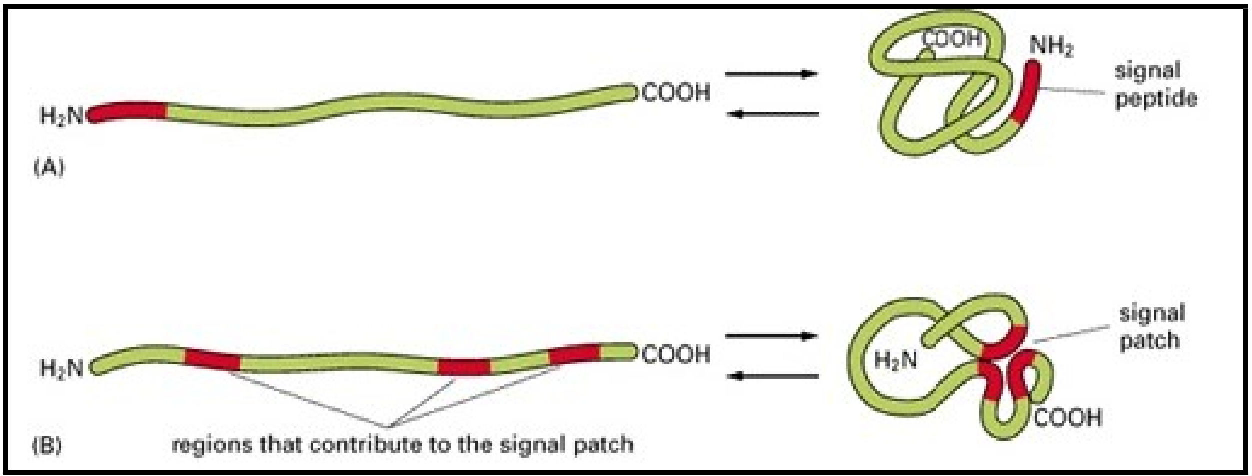

Figure 3.2 Nascent Protein molecules with its signal peptides and signal patches to modified. *Source-Albert et al.*

Mechanisms of Protein Sorting

Different types of signal peptides are used to specify different destinations in the cell. Proteins destined for initial transfer to the ER usually have a signal peptide at their amino terminus, which characteristically includes a sequence composed of about 5 to 10 hydrophobic amino acids. Most of these proteins will in turn pass from the ER to the Golgi apparatus, but those with a specific sequence of four amino acids at their carboxyl terminus are retained as permanent ER residents. Proteins destined for mitochondria have signal peptides of yet another type, in which positively charged amino acids alternate with hydrophobic ones. Proteins destined for peroxisomes usually have a specific signal sequence of three amino acids at their carboxyl terminus. Many proteins destined for the nucleus carry a signal peptide formed from a cluster of positively charged amino acids, which is commonly found at internal sites of the polypeptide chain. Some typical signal peptides are listed in **Table 3.1**

Table 3.1-Given important peptide sequences of proteins and their imported sites

S. No.	Function of Signal Peptide	Example of Signal Peptide
1	Import into ER	$^{+}H_{3}N$-Met-Met-Ser-Phe-Val-Ser-Leu-Leu-Leu-Val-Gly-Ile-Leu-Phe-Trp-Ala-Thr-*Glu*-Ala-*Glu*-Gln-Leu-Thr-**Lys**-Cys-*Glu*-Val-Val-Phe-Gln-
2.	Retain in lumen of ER	-**Lys**-*Asp*-*Glu*-Leu-COO^{-}
3.	Import Into Mitochondria	$^{+}H_{3}N$-Met-Leu-ser-**Arg**-Gln-Ser-Ile-**Agr**-Gln-Ser-Phe-Phe-**Lys**-Pro-Ala-Thr-**Arg**-Thr-Leu-Cys-ser-Ser-**Arg**-Tyr-Leu-Leu-
4.	Import to Nucleus	Pro-Pro-**Lys**-**Lys**-**Lys**-**Arg**-**Lys**-Val
5	Import to Peroxisome	Ser-**Lys**-Leu-
6.	Attach to membrane *via* the covalent linkage of a myristic acid to the amino terminus	$^{+}H_{3}N$-Gly-ser-Ser-**Lys**-**Ser**-Pro-**Lys**-
	Positively Charged amino acids shown in Bold and negatively charged in Italic. An extended block of amino acids is underlined, $^{+}H_{3}N$ indicates the amino terminus of a protein; COO^{-} indicates the carboxy terminus	

Concept of Protein Targeting

The signal peptides and signal patches have decided to further transport to be carried to their destination by **protein targeting.** The signal of amino acids sequences are easily transported to their destination organelles that are easily studied but the signal patches are modified after that for further transport which is very complicated due to a complex three-dimensional protein-folding pattern, they cannot be easily transferred experimentally from one protein to another. So the protein targeting can be considered a further step of protein transport after protein sorting or can be studied under a similar heading as **Protein sorting and targeting.** Therefore the previously discussed three ways of transport of protein to their respective destination are followed by different methods as further discussion.

Protein Targeting to the Nucleus

The protein traffic between the cytosol and nucleus occurs between topologically equivalent spaces, which are in continuity through the nuclear pore complexes. This process is called **gated transport** because the nuclear pore complexes function as selective gates that can actively transport specific macromolecules and macromolecular assemblies, although they also allow free diffusion of smaller molecules. In some cases the transport process is complex: ribosomal proteins, for instance, are made in the cytosol, imported into the nucleus - where they assemble with newly made ribosomal RNA into particles - and then exported again to the cytosol as part of a ribosomal subunit; each of these steps involves selective transport across the nuclear envelope.

Brief Pathway of Protein Import to or Export from Nucleus

Bidirectional transport of protein occurs continuously between the cytosol and the nucleus through gate transporter or **nuclear pore**. The many proteins that function in the nucleus - including histones, DNA and RNA polymerases, gene regulatory proteins, and RNA-processing proteins - are **selectively imported** into the nuclear compartment from the cytosol where they are made. At the same time, tRNAs and mRNAs are synthesized in the nuclear compartment and then exported to the cytosol. Like the import process, the export process is selective; mRNAs, for example, are exported only after they have been properly modified by RNA-processing reactions in the nucleus. Proteins imported to or exported from the nucleus contain a specific amino acid sequence (Pro-Lys-Lys-Lys-Arg-Lys-Val) that functions as a **nuclear-localization signal** (**NLS**) or a **nuclear-export signal** (**NES**).

Nucleus-restricted proteins contain an NLS but not an NES, whereas proteins that shuttle between the nucleus and cytoplasm contain both signals. Several different types of NES and NLS have been identified. Each type of nuclear transport signal is thought to interact with a specific receptor protein of **exportin** or **importin** (□ and □ subunit of) belonging to a family of homologous proteins termed **karyopharins**. These signal transporting proteins bind to a carrier protein known as "**cargo**" . A cargo protein bearing an NES or NLS translocates through nuclear pores bound to its cognate receptor protein (karyopharin), which also interacts with FG-nucleoporins (sequences rich in phenylalanine,F) and glycine, G) residues . Importins and exportins are thought to diffuse through the channel by binding transiently to different FG-repeats that act like "stepping stones' ' through the pore. Both transport processes also require participation of Ran, a monomeric G protein that exists in different conformations when bound to GTP or GDP.

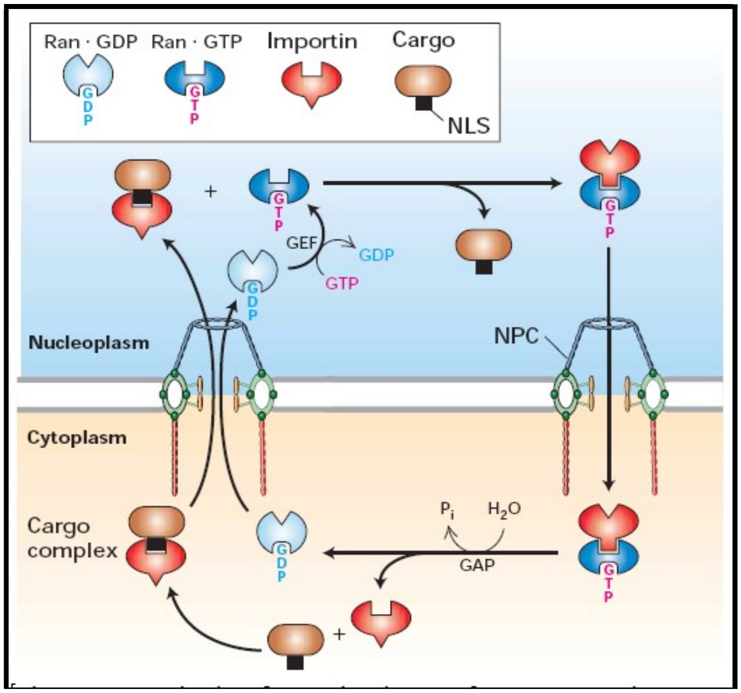

Figure 3.3 Mechanism of Nuclear Import of "Cargo" Protein. *Source Lodish et al*.

After a cargo complex reaches its destination (the cytoplasm during export and the nucleus during import), it dissociates, freeing the cargo protein and other components.The latter then are transported through nuclear pores in the reverse direction to participate in transporting additional molecules of cargo protein.

ProteinsTargeting to Mitochondria

Most mitochondrial and chloroplast proteins are encoded by nuclear genes, synthesized on cytosolic ribosomes, and imported post-translationally into the organelles. These mitochondrial precursor proteins almost always have a signal peptide (20-80 residues long) at their amino terminus that is rapidly removed after import by a protease (the signal peptidase) in the mitochondrial matrix. The signal peptides can be remarkably simple. These 12 residues can be attached to any cytosolic protein and will direct the protein into the mitochondrial matrix and are amphipathic alpha-helical structures in which positively charged residues are clustered on one side of the helix while uncharged hydrophobic residues are clustered on the opposite side. This configuration is thought to be recognized by specific receptor proteins on the mitochondrial surface.

Brief Pathway of Proteins Transport to Mitochondria and Chloroplasts

All the information required to target a precursor protein from the cytosol to the mitochondrial matrix or chloroplast stroma is contained within its N-terminal uptake-targeting sequence. The step by step mechanism is given below as predicted in figure 3.4

Step 1. Precursor proteins synthesized on cytosolic ribosomes are maintained in an unfolded or partially folded state by bound chaperones, such as Hsc70 (Heat shock cognate protein that makes protein in strait). The binding of Hsc70 needs one ATP.

Step 2. After a transporting protein binds to an import receptor by its signal sequences (-----$^+NH_3$)near a site of contact with the inner membrane.

Step 3. It is then transferred into the general import pore of mitochondria.

.

Step 4 - 5. The translocating protein then moves through this pore which is made up of Tom20 and Tom22 (Proteins in the outer mitochondrial membrane involved in targeting and import are designated Tom proteins for translocation of the outer membrane). and an adjacent channel in the inner membrane. This type of pore is situated where the outer and inner membrane has minimum spaces.

Step 6. When the transporting protein reaches the matrix, uptake-targeting sequence is removed by a matrix protease and Hsc70 is released from the newly imported protein.

Step 7. It folds into the mature, active conformation within the matrix. Further folding of protein is done by matrix chaperonins.

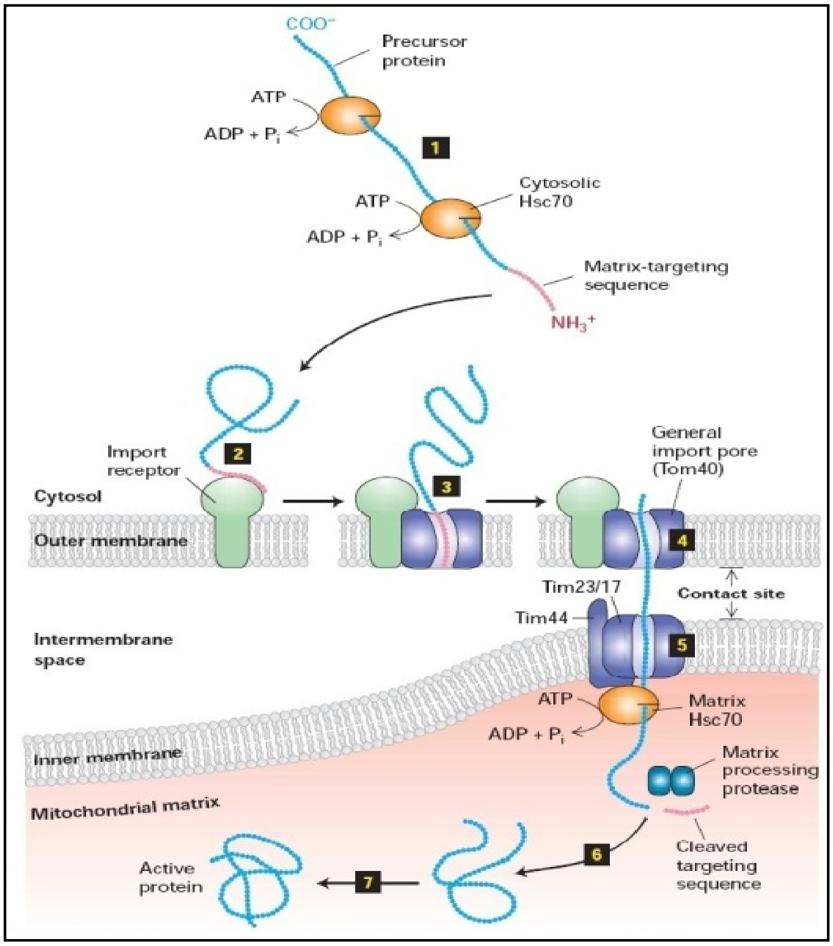

Figure 3.4 Protein import to Mitochondrial Matrix.
Source – Lodish et al.

Protein targeting to Peroxisomes

Peroxisomes are small cell organelles bounded by a single membrane. Unlike mitochondria and chloroplasts, peroxisomes lack DNA and ribosomes. Thus all peroxisomal proteins are encoded by nuclear genes, synthesized on ribosomes free in the cytosol, and then incorporated into preexisting or newly generated peroxisomes. As peroxisomes are enlarged by addition of protein (and lipid), they eventually divide, forming new ones, as is the case with mitochondria and chloroplasts.

The size and enzyme composition of peroxisomes vary considerably in different kinds of cells. However, all peroxisomes contain enzymes that use molecular oxygen to oxidize various substrates, forming hydrogen peroxide (H_2O_2). Catalase, a peroxisome-localized enzyme, efficiently decomposes H_2O_2 into H_2O. Peroxisomes are most abundant in liver cells, where they constitute about 1 to 2 percent of the cell volume.

The proteins that have to transport into the Peroxisome have the **signal sequence Ser- Lys-Leu (SKL in one-letter code)** or a related sequence at the C-terminus was necessary for peroxisomal targeting. Further, addition of the SKL sequence to the C-terminus of a normally cytosolic protein leads to uptake of the altered protein by peroxisomes in cultured cells. All but a few of the many different **peroxisomal matrix proteins** bear a sequence of this type, known as *peroxisomal-targeting sequence 1, or simply PTS1*.

Brief Pathway of Protein Targeting to Peroxisome

The pathway for import of catalase and other PTS1- bearing proteins into the peroxisomal matrix is depicted in below Figure as step by step

Step 1. Catalase and most other peroxisomal proteins contain a C-terminal PTS1 uptake-targeting sequence (red) that binds to the cytosolic receptor Pex5.

Step 2. Pex5 with the bound matrix protein interacts with the Pex14 receptor located on the peroxisome membrane.

Step 3. The matrix protein–Pex5 complex is then transferred to a set of membrane proteins (Pex10, Pex12, and Pex2) that are necessary for translocation into the peroxisomal matrix by an unknown mechanism.

Step 4. At some point, either during translocation or in the lumen, Pex5 dissociates from the matrix protein and returns to the cytosol, a process that involves the Pex2/10/12 complex and additional membrane and cytosolic proteins not shown.

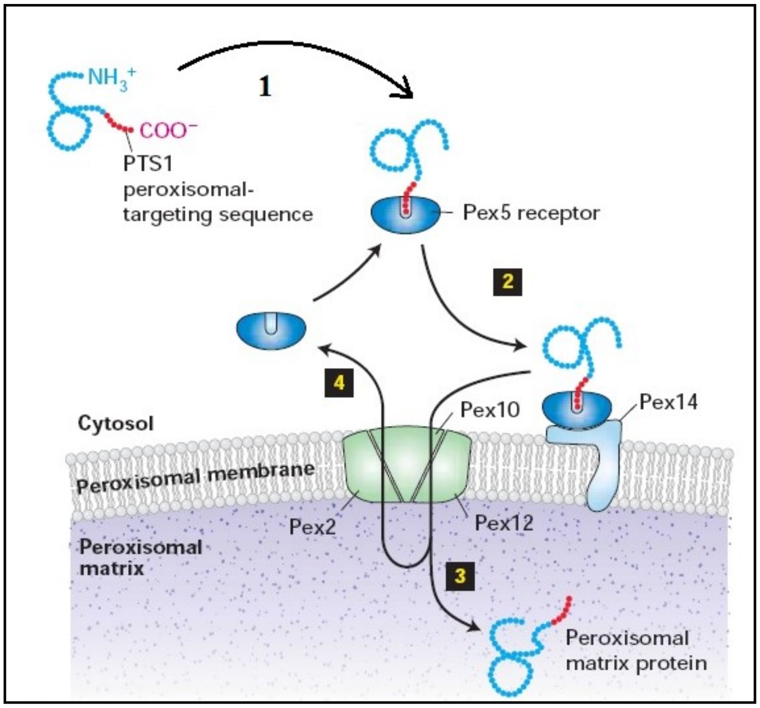

Figure 3.5 **Import of cytosomal protein to Peroxisomal matrix.**
Source Lodish et al.

Cytoplasmal proteins are of two types. The first types are without specific signals and second types that have a specific signal for caring for the ER transport. These types of protein have a recognition signal of **hydrophobic amino acids located at the N-terminus** that is generally known as **ER signal sequence** which are the tag or shorting signal and these ER signals were formed in the starting of translation of protein at nascent stage. These proteins entering the endoplasmic reticulum are initiated on free ribosomes. A targeting **ER signal** sequence of Proteins further followed two pathways.

1. Proteins having ER Signal cleaved by the ER enzymes and are completely translocated into the lumen of endoplasmic reticulum. These proteins are soluble (not membrane proteins) and are destined for secretion, or for transfer to golgi bodies and lysosomes. In all of these cases the proteins are never part of membranes **and further follow the pathway of Secretory transport within the cytoplasm.**
2. Proteins having ER Signal cleaved by the ER enzymes, but are inserted into membranes by specific **stop codon** and are known as **integral (transmembrane) proteins**, Therefore these types of proteins are partially translocated into the endoplasmic reticulum. These proteins may be destined for ER, membranes of another organelle (Golgi, lysosomes or endosomes), or the plasma membrane. These types of proteins further follow a pathway of transport called **vesicular transport (Endocytosis and Exocytosis).**

Secretory (Cotranslational) Pathway of proteinsTargeting to ER lumen

The protein having ER signal first of all binds to a receptor protein **signal-recognition particle** (**SRP**) that located it on the ER membrane. The SRP is a cytosolic ribonucleoprotein particle that transiently binds to the ER signal sequence in a nascent protein, even under the process of transcription (during the early stage of protein formation) and therefore also referred to as **Cotranslational transport**. The process is very complicated hence the complete pathway is explains under the following steps-

Step 1-2. Once the ER signal sequence emerges from the ribosome, it is bound by a signal-recognition particle (SRP).

Step 3. The SRP delivers the ribosome/nascent polypeptide complex to the SRP receptor in the ER membrane. This interaction is strengthened by binding of GTP to both the SRP and its receptor.

Step 4. Transfer of the ribosome/nascent polypeptide to the translocon leads to opening of this translocation channel and insertion of the signal sequence and adjacent segment of the growing polypeptide into the central pore. Both the SRP and SRP receptor, once dissociated from the translocon, hydrolyze their bound GTP and then are ready to initiate the insertion of another polypeptide chain.

Step 5. As the polypeptide chain elongates, it passes through the translocon channel into the ER lumen, where the signal sequence is cleaved by and is rapidly degraded.

Step 6. The peptide chain continues to elongate as the mRNA is translated toward the 3 end. Because the ribosome is attached to the translocon, the growing chain is extruded through the translocon into the ER lumen.

Steps 7-8. Once translation is complete, the ribosome is released, the remainder of the protein is drawn into the ER lumen, the translocon closes, and the protein assumes its native folded conformation.

When these types of Soluble proteins accumulate into the ER lumen, then transfer to the lumen of other organelles such as golgi bodies or lysosomes and secreted out of the cell by secretory vesicles.

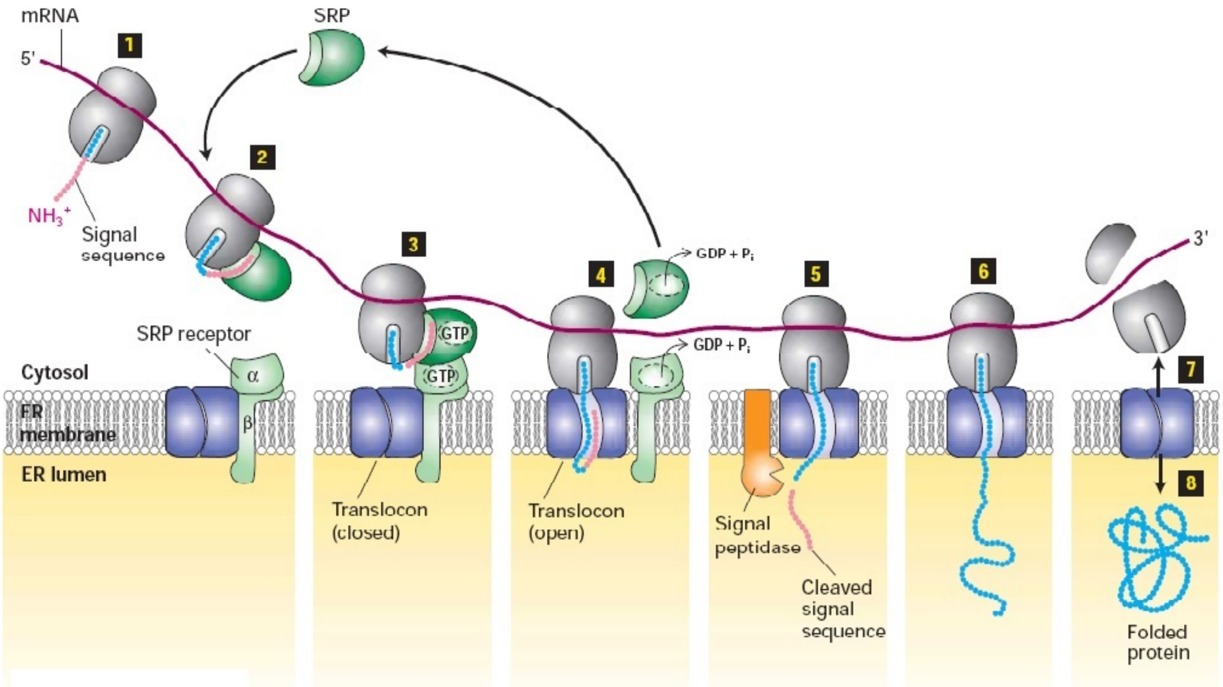

Figure 3.6- Synthesis of secretory proteins and their cotranslational translocation across the ER membrane.
Source - Lodis *et al*

Cotranslational transport and Post translational transport of Protein

The pathway of protein transport or targeting is called **Cotranslational transport** or targeting when the protein targeting pathway is started while the translation of nascent protein is still in process (during the early stage of protein formation). **Post translational transport** is started after the protein translation is over and nascent protein is formed in the cytosol. In cotranslational translocation, the **signal-recognition particle** (**SRP**) first recognizes and binds the ER signal sequence on a nascent secretory protein and in turn is bound by an SRP receptor on the ER membrane, thereby targeting the ribosome/nascent chain complex to the ER. The SRP and SRP receptor then mediate insertion of the nascent secretory protein into the **translocon** (pore complex of ER by which protein is inserted into the lumen of ER). Hydrolysis of GTP by the SRP and its receptor is needed to drive this docking process. As the ribosome attached to the translocon continues translation, the unfolded protein chain is extruded into the ER lumen. No additional energy is required for Cotranslocational transport of protein.

In post-translational translocation, a completed secretory protein is targeted to the ER membrane by interaction of the signal sequence with the translocon. The polypeptide chain is then pulled into the ER by a ratcheting mechanism that requires ATP hydrolysis by the **chaperone BiP**, which stabilizes the entering polypeptide . In both cotranslational and post-translational translocation, a signal peptidase in the ER membrane cleaves the ER signal sequence from a secretory protein soon after the N-terminus enters the lumen.

Targeting of (transmembrane) Proteins to the ER

Integral (transmembrane) proteins are always present in the plasma membrane and other cellular membranes (as have been explained in the first chapter) . Each such protein has a unique orientation with respect to the membrane's phospholipid bilayer. Integral proteins located in ER, Golgi, and lysosomal membranes and in the plasma membrane, which are synthesized on the rough ER, remain embedded in the membrane as they move to their final destinations along the same pathway followed by soluble secretory proteins (as mentioned above). The further process is very complicated and follows different pathways on the basis of signals of that protein called **hydrophobic stop-transfer anchor sequence** which are in the form of Type I, II, III and IV. These signals are responsible for inserting it into the plasma membrane which is beyond the standard of students. The insertion of protein has tried to explain in regard to Type I protein step by step below

Brief Pathway of Protein - Type I (transmembrane) Targeting to the ER

Step 1. After the ribosome/nascent chain complex becomes associated with a translocon in the ER membrane, the N-terminal signal sequence is cleaved. This process occurs by the same mechanism as the one for soluble secretory proteins (see Figure 16-6).

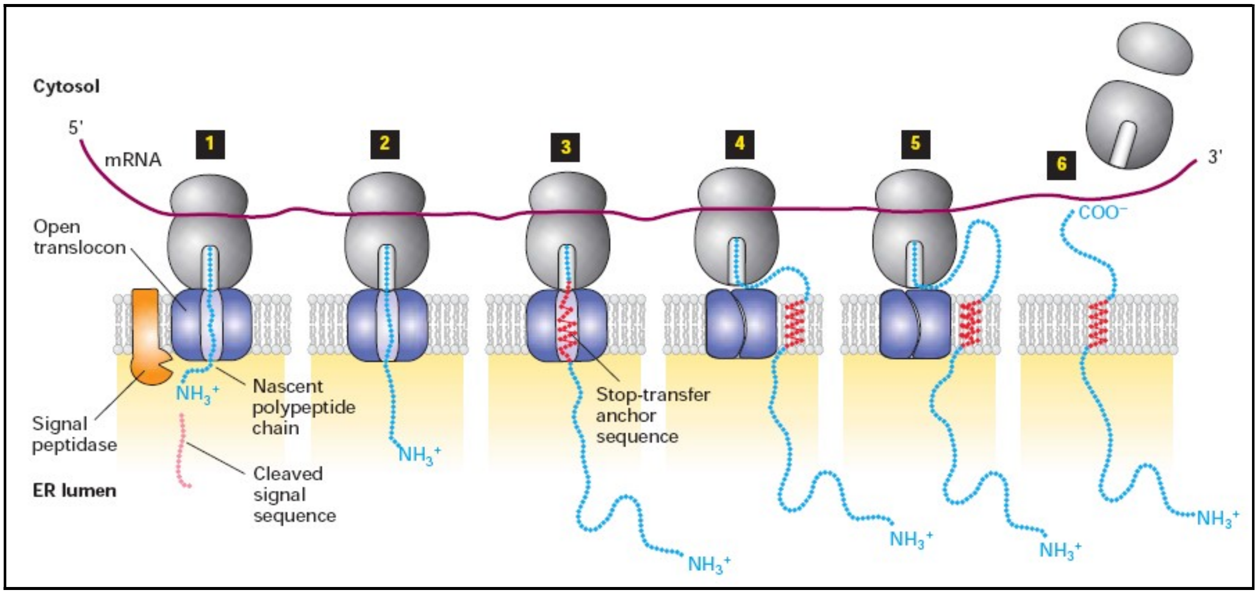

Figure 3.7- Synthesis and insertion of Type – I single pass protein into the ER Membrane
Source – Lodish et al

Steps 2 -3. The chain is elongated until the **hydrophobic stop-transfer anchor sequence** is synthesized and enters the translocon, where it prevents the nascent chain from extruding farther into the ER lumen.

Step 4. The stop-transfer anchor sequence moves laterally between the translocon subunits and becomes anchored in the phospholipid bilayer. At this time, the translocon probably closes.

Step 5. As synthesis continues, the elongating chain may loop out into the cytosol through the small space between the ribosome and translocon.

Step 6. When synthesis is complete, the ribosomal subunits are released into the cytosol, leaving the protein free to diffuse in the membrane.

Exocytosis and Endocytosis - A Pathway of Vesicular Trafficking

By the above mentioned pathway, the soluble protein accumulated in the lumen of ER and transmembrane protein inserted into the membrane. When these types of protein are aggregated in the ER, they are further transported to golgi bodies or to final destination (lysosome, endosome by the budding off in package “cargo” through another type of pathway known as **vesicular trafficking.**

After budding from the trans-Golgi network, **the first type of vesicle** immediately moves to and fuses with the plasma membrane, releasing its contents by **exocytosis**. In all cell types, at least some proteins are loaded into such vesicles and secreted continuously in this manner. Examples of proteins released by such constitutive (or continuous) secretion include collagen

by fibroblasts, serum proteins by hepatocytes, and antibodies by activated B lymphocytes. **The second type of vesicle to bud** from the trans-Golgi network, **known as secretory vesicles**, are stored inside the cell until a signal for exocytosis causes release of their contents at the plasma membrane. Among the proteins released by such regulated secretion are peptide hormones (e.g., insulin, glucagon, ACTH) from various endocrine cells, precursors of digestive enzymes from pancreatic acinar cells, milk proteins from the mammary gland, and neurotransmitters from neurons.

The third type of vesicle that buds from the trans-Golgi network is directed to the **lysosome**, an organelle responsible for the intracellular degradation of macromolecules, and to

lysosome-like storage organelles in certain cells. It may involve direct fusion of the endosome with the lysosomal membrane. Soluble proteins delivered by this pathway include lysosomal digestive enzymes (e.g., proteases, glycosidases, and phosphatases) and membrane proteins (e.g., V-class proton pump) that pump H from the cytosol into the acidic lumen of the endosome and lysosome.

The endosome also functions in the endocytic pathway in which vesicles bud from the plasma membrane bringing membrane proteins and their bound ligands into the cell (see Figure 17-1). After being internalized by **endocytosis**, some proteins are transported to lysosomes, while others are recycled back to the cell surface. Endocytosis is a way for cells to take up nutrients that are in macromolecular form—for example, cholesterol in the form of lipoprotein particles and iron complexed with the serum protein transferrin. Endocytosis also can function as a regulatory mechanism to decrease signaling activity by withdrawing receptors for a particular signaling molecule from the cell surface.

Brief Pathway of the Exocytic and Endocytic by Vesicular Trafficking

This pathway of protein targeting is very complex and sorted proteins for their final destination by macular level of interactions. The step by step has been demonstrated in figure by avoiding signal shorting complications.

Step 1: Synthesis of proteins bearing an ER signal sequence is completed on the rough ER

Step 2: The newly made polypeptide chains are inserted into the ER membrane or cross it into the lumen. Some proteins (e.g., ER enzymes or structural proteins) remain within the ER. The remainder are packaged into transport vesicles.

Step 3: that bud from the ER and fuse together to form new cis-Golgi cisternae. Missorted ER-resident proteins and vesicle membrane proteins that need to be reused are retrieved to the ER by vesicles

Step 4: that bud from the cis-Golgi and fuse with the ER. Each cis-Golgi cisterna, with its protein content, physically moves from the cis to the trans face of the Golgi complex

Step 5: by a nonvesicular process called cisternal progression. Retrograde transport vesicles

Step 6: move Golgi-resident proteins to the proper Golgi compartment. In all cells, certain soluble proteins move to the cell surface in transport vesicles

Step 7: and are secreted continuously (constitutive secretion). In certain cell types, some soluble proteins are stored in secretory vesicles

Step 8: and are released only after the cell receives an appropriate neural or hormonal signal (regulated secretion). Lysosome-destined membrane and soluble proteins, which are transported in vesicles that bud from the trans-Golgi

Step 9: first move to the late endosome and then to the lysosome. Endocytic pathway: Membrane and soluble extracellular proteins taken up in vesicles that bud from the plasma membrane and also can move to the lysosome via the endosome.

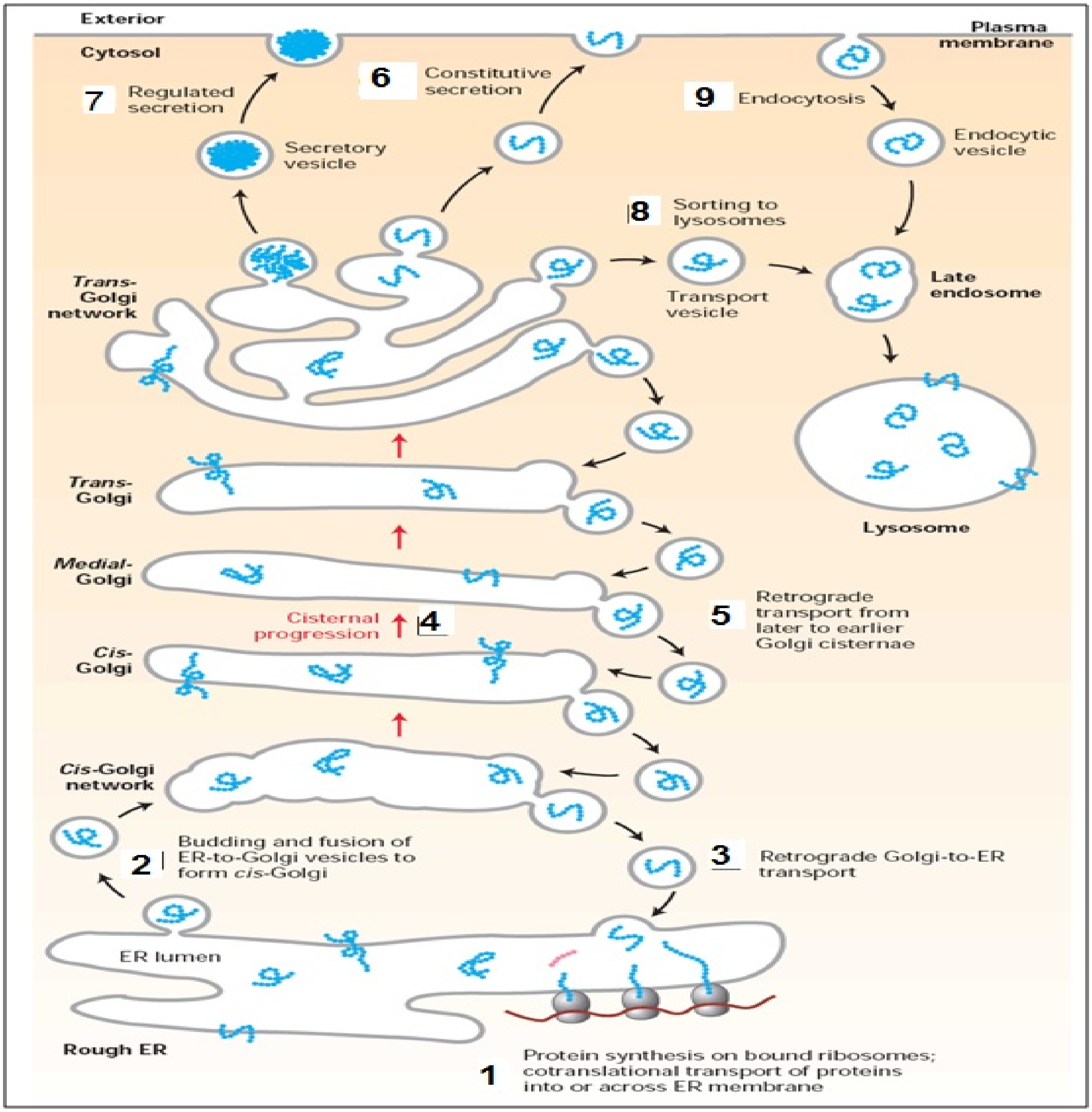

Figure 3.8- Overview of Secretory (Exocytic) and Endolytic pathway of Protein Source –*Lodish et al*.

Molecular Mechanisms of Vesicular Trafficking

Small membrane-bounded vesicles that transport proteins from one organelle to another are common elements in the secretory, exocytosis and endocytic pathways (as discussed earlier).

These vesicles bud from the membrane of a particular "parent" (donor) organelle and fuse with the membrane of a particular "target" (destination) organelle. Although budding of vesicles from ER and fusion to golgi cisternae is very specific and uses molecular level of sorting and transporting vesicle cargo for its adject location.

The budding of vesicles from their parent membrane is driven by the polymerization of soluble protein complexes onto the membrane to form a proteinaceous vesicle coat (Figure 17-7a). Interactions between the cytosolic portions of integral membrane proteins and the vesicle coat gather the appropriate cargo proteins into the forming vesicle. Thus the coat not only adds curvature to the membrane to form a vesicle but also acts as the filter to determine which proteins are admitted into the vesicle.

The integral membrane proteins in a budding vesicle include **v-SNAREs** : ***V***esicle - ***S***oluble ***N***SF (N-Ethylmaleimide-Sensitive) ***A***ttachment proteins ***Re***ceptor, which are crucial to eventual fusion of the vesicle with the correct target membrane. Shortly after formation of a vesicle is completed, the coat is shed exposing its v-SNARE proteins. The specific joining of v-SNAREs in the vesicle membrane with cognate t-SNAREs in the target membrane brings the membranes into close apposition, allowing the two bilayers to fuse.

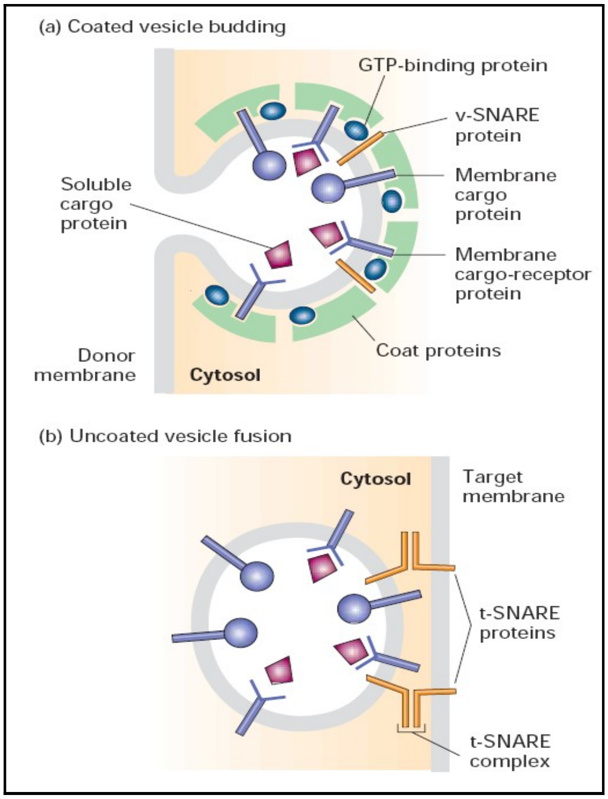

Figure 3.9- Overview of Vesicle budding and fusion with a target membrane. *Source- Lodish et al.*

Protein Coat targeting of Vesicle Cargo

Three types of coated vesicles have been characterized, each with a different type of protein coat and each formed by reversible polymerization of a distinct set of protein subunits. Each type of vesicle, named for its primary coat proteins, transports cargo proteins from particular parent organelles to particular destination organelles:

1. **COPII** (***Co***atomer **P**rotein) vesicles transport proteins from the rough ER to the Golgi.

2. **COPI vesicles** mainly transport proteins in the retrograde direction between Golgi cisternae and from the cis-Golgi back to the rough ER.

3. **Clathrin vesicles** transport proteins from the plasma membrane (cell surface) and the trans-Golgi network to late endosomes.

Pathway of Protein Coated Vesicular Trafficking (E R to Golgi bodies and *vis -a vis,* Figure 3.10)

Steps 1– 3: Forward (anterograde, From ER to Golgi cis) transport is mediated by COPII vesicles, which are formed by polymerization of soluble COPII coat protein complexes (blue) on the ER membrane. v-SNAREs (red) and other cargo proteins (green) in the ER membrane are incorporated into the vesicle by interacting with coat proteins. Soluble cargo proteins (purple) are recruited by binding to appropriate receptors in the membrane of budding vesicles. Dissociation of the coat recycles free coat complexes and exposes v-SNARE proteins on the vesicle surface. After the uncoated vesicle becomes tethered to the cis-Golgi membrane in a Rab-mediated process, pairing between the exposed v-SNAREs and cognate t-SNAREs in the Golgi membrane allow vesicle fusion, releasing the contents into the cis-Golgi compartment. **(Figure 3.10)**

Steps –4-6: Reverse (retrograde) transport, mediated by vesicles coated with COPI proteins (green), recycles the membrane bilayer and certain proteins, such as v-SNAREs and missorted ER-resident proteins (not shown), from the cis- Golgi to the ER. All SNARE proteins are shown in red although each v-SNARE and t-SNARE are distinct proteins **(Figure 3.10)**

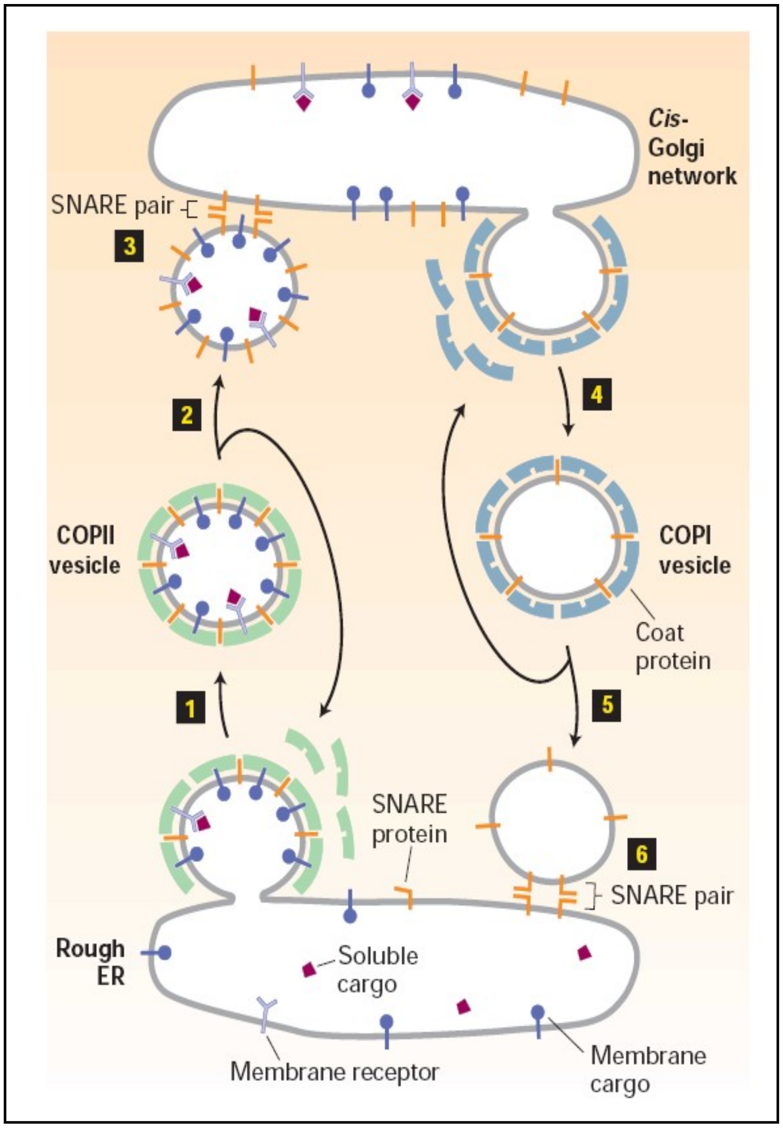

Figure 3.10-Vesicle Coated Protein trafficking between the ER and cis Golgi. *Source-Lodish et al.*

Chapter 4

Introduction to all national and international Biologists (Zoologists) who have contributed/contributing to Zoological and Life Sciences as a mark of tribute to ancient and modern biology will be included as part of the Continuous Internal Evaluation (CIE)

Indian Civilization and Biology

The Indian subcontinent has remains of early, middle and late stone ages (4,00,000- 2,00,000 BC). The major breakthrough occurred between 12,000 -10,000 years ago when domestication of plants and animals began resulting in development of agriculture and animal husbandry. The earliest cultivated plants were Wheat, Barley, Lentil and Pea.

Cultivation of Rice and Cotton began almost simultaneously. **Mehrgarh** and **Mahagarh** are believed to be centres of origin of cultivation of Rice about 6000 years ago. Cultivated Rice evolved from Wild Rice that originated somewhere along the coast of Bay of Bengal comprising Bengal, Orissa and Andhra Pradesh. Ancient Indians developed a number of rice varieties (about 1,00,000). Some of these varieties were resistant to salt and flooding. Nutritive and fragrant varieties were also developed at that time. A number of domesticated animals were raised, e.g, cattle, goat, sheep, pig, dog. Naturally, raising cultivated plants and domesticated animals required a good amount of knowledge and scientific attitude.

Biology in the Vedic Period (2500-650 BC)

The natural sciences were well rooted in the Vedic periods and studied the various types of plants, animals and happenings of nature. The names of 740 plants and 250 animals have been reported in Vedas.

Chandyogya Upanishad has classified animals into 3 categories **Jivaji** (viviparous), **Andaja** (oviparous) and **Udbhija** (vegetal origin). **Jivaji** included mammals. Birds, Reptiles, Insects, Worms etc. were included under Andaja. Udbhija contained small animals.

Dhanvantri is regarded as the **god of medicine**. The earliest famous medical men of vedic times were **Ashvini Kumars**. The most famous men of the post vedic period were **Susruta of Kashi** and **Atreya in Taxila**. **Susruta was a surgeon and is called the father of Indian surgery**.

Atreya

Atreya was a man of medicine (both about 600 BC). Atreya's work was compiled by his pupil, Agnivesa, which was revised by Charka (100 BC) in his famous book ``Charka Samhita".

Ayurveda is the name of indigenous system of medicine in India. It literally means the science of living long (Sans, ayu longevity of life. veda knowledge). It is largely derived from the concept of doshas. Some work on the origin and evolution of life was undertaken by ancient Indians. Ayurveda mentions the origin of life. **Taittiriya Upnishad** (Ca 7-8 BC) has traced the origin of life to space. Manusmriti or Manu Samhita (200 AD) has also proposed evolution. Charka and other intellectuals of ancient India believed living beings including man to be formed of 6 elements prithvi (earth), ap (water or liquid), teja (fire), vayu (air), akasa (ether) and brahman (spirit).

Sushruta

Sushruta was an **ancient Indian scientist and a physician** known for his book **Susruta Samhita**. He investigated human anatomy with the help of a dead body. In his book, he mentioned over 1100 diseases including fevers of 26 kinds, jaundice of 8 kinds, and urinary complaints of 20 kinds. More than 760 plants are described and its all parts including roots, bark, juice, resin, flowers, etc as remedies. In Susruta Samhita there is a description of 101 different instruments used in surgery. He also described some of the serious operations performed like taking the fetus out of the womb, repairing the damaged rectum, removing stone from the bladder, and many more. **Shusruta is referred to as the Father of Surgery**. **Susruta of Kashi** (Susruta Samhita 600 BC) classified living beings into **sthavara** (immobile e.g., plants) and **jangma** (mobile e.g., animals). **Susruta** divided plants into 4 categories (a) **Osadhi**. Monocarpic plants (b) **Virudha**. Shrubs and creepers. (c) **Vrksa**. Fruit yielding flowering plants. (d)

Vanaspati. Fruit yielding "nonflowering plants" Plant parts were also described as **phala** (fruit), **puspa** (flower) **, patra** (leaf), **mula** (root), **kanda** (bulb or stem) and **ankura** (sprout). Animals were classified into **guhasaya** (carnivorous quadrupeds, e.g. tiger, lion), **jangla** (herbivorous quadrupeds of forest, e.g., deer), **kulacara** (herbivores frequenting banks of water body, e.g., buffalo, elephant) and **matsya** (fish). Other animals mentioned by Susruta are leeches and both poisonous as well as non- poisonous snakes.

Charka (100 BC)

Charka was considered the father of ancient Indian science of medicine. Charka was one of the major contributors to Ayurveda. Charaka was the royal doctor in the Kanishka's court. **Charka** is considered the first-ever physician to preface the idea of digestion, metabolism, and immunity. He elaborated in his book Charka Samhita, the body functions because it comprises three dosha or principles, namely movement (vata), transformation (pitta), and lubrication & stability (kapha). Additionally, he emphasized, illness is caused when the balance among the Har Gobind Khorana three doshas in a human body is disturbed. To restore the balance he prescribed ayurvedic medicines. **Charka (100 BC) laid down the concept of digestion**, **metabolism and immunity**. **He knew fundamentals of genetics including factors determining sex of a child**.

Varahamihira

He had made great contributions in the fields of hydrology, geology, maths and **ecology**. First scientist who claim that termites and plants could be the indicators of the presence of underground water. In fact he had given important information about termites (insects that destroy woods or dimak) that they go very deep to the surface of water level to bring water to keep their houses wet.In his **Brhat Samhita** he had given **earthquake cloud theory** which has attracted the world of science.

Maharishi Patanjali

He is known as **Father of Yoga** who had compiled 195 Yoga Sutras. He was the first who had systematically presented Yoga as the great science. In Patanjali's Yoga Sutras, Aum is spoken as a symbol of God. He refers to Aum as a cosmic sound. **He also wrote a work on medicine and worked** on Panini's grammar known as Mahabhasaya. **It is believed that he is an essayist who had written upon the ancient Indian medicine system i.e. Ayurved.** It is believed that the Jeeva Samadhi of Patanjali is situated at Tirupattur Brahmapureswara Temple.

Modern Indian Biologist

Jagadish Chandra Bose (1858 - 1937)

Considered the father of Bengali science fiction, Jagadish Chandra Bose was born in Mymen singh in the Bengal Presidency (in present-day Bangladesh) on 30th November 1858. **His contributions to plant science are significant, such as the invention of the crescograph, a device that could measure the growth of plants**. He also played a pioneering role in the investigation of radio and microwave optics. He was one of the few scientists who were opposed to patenting any of his inventions. To honour him, a crater has been named after him on the moon. J. C. Bose died on 23rd November 1937.

Birbal Shahni (1891 – 1949)

Birbal Sahni (14 November 1891 – 10 April 1949) **was an Indian paleobotanist who studied the fossils of the Indian subcontinent**. He also took an interest in geology and archaeology. He founded what is now the Birbal Sahni Institute of Palaeobotany at Lucknow in 1946. His major contributions were in the study of the fossil plants of India and in plant evolution. He was also involved in the establishment of Indian science education and served as the President of the National Academy of Sciences, India and as an Honorary President of the International Botanical Congress, Stockholm.

Janaki Ammal Edavalath Kakkat (1897 – 1984)

She (4 November 1897 – 7 February 1984) was an Anglo-Indian botanist who worked on plant breeding, cytogenetics and phytogeography. Her most notable work involved studies on sugarcane and the eggplant (brinjal). She also worked on the cytogenetics of a range of plants and co-authored the *Chromosome Atlas of Cultivated Plants* (1945) with C.D. Darlington. She took an interest in ethnobotany and in plants of medicinal and economic value from the rain forests of Kerala, India. She was awarded a **Padma Shri by the Indian government in 1977.**

Salim Ali (1896 – 1987)

Popular as the Birdman of India, Salim Moizuddin Abdul Ali was born on the 12th of November, 1896 in Bombay, Maharashtra. A naturalist and ornithologist, **Salim Ali was the first Indian who conducted systematic surveys on birds across India**. He played an important role in the establishment of the Bharatpur bird sanctuary (Keoladeo National Park), along with contributing to the development of the Bombay Natural History Society which made him one of the profound Indian scientists. He became a key figure behind the Bombay Natural History Society after 1947. For his contributions, the Indian Government awarded him with the Padma Bhushan and the Padma Vibhushan in 1958 and 1976 respectively. **He wrote the ten-volume Handbook of the Birds of India and Pakistan in association with the American ornithologist, Sidney Dillon Ripley**. Salim Ali died on the 20 of June 1987.

Gopalasamudram Narayanan Ramachandran (1922 – 2001)

G.N. Ramachandran, (8 October 1922 – 7 April 2001) was an Indian physicist who was known for his work that led to his creation of the **Ramachandran plot for understanding peptide structure**. **He was the first to propose a triple-helical model for the structure of collagen**. He subsequently went on to make other major contributions in biology and physics. Notable awards that Ramachandran received include the Shanti Swarup Bhatnagar Award for Physics in India (1961) and the Fellowship of the Royal Society of London. In 1999, the International Union of Crystallography honoured him with the Ewald Prize for his 'outstanding contributions to crystallography'. He was nominated for the Nobel Prize as well for his fundamental contributions in protein structure and function.

Har Gobind Khorana (1922 – 2011)

H G Khorana was an Indian American biochemist. While on the faculty of the University of Wisconsin–Madison, he shared the 1968 Nobel Prize for Physiology or Medicine with Marshall W. Nirenberg and Robert W. Holley for research that showed the order of nucleotides in nucleic acids, which carry the genetic code of the cell and control the cell's synthesis of proteins. Their Nobel lecture was delivered on 12 December 1968. **Khorana was the first scientist to chemically synthesize oligonucleotides**. This achievement, in the 1970s, was also the **world's first synthetic gene**; in later years, the process has become widespread. Subsequent scientists referred to his research while advancing genome editing.

These synthetic genes by using polymerase and ligase enzymes that link pieces of DNA together, as well as methods that anticipated the invention of polymerase chain reaction (PCR). These custom-designed pieces of artificial genes are widely used in biology labs for sequencing, cloning and engineering new plants and animals, and are integral to the expanding use of DNA analysis to understand gene-based human disease as well as human evolution.

Dr Lalji Singh (1947 – 2017)

Lalji Singh (5 July 1947 – 10 December 2017) was an Indian scientist who worked in the field of DNA fingerprinting technology in India, where he was popularly known as the "**Father of Indian DNA fingerprinting**". Singh also worked in the areas of molecular basis of sex determination, wildlife conservation forensics and evolution and migration of humans. In 2004, he received the **Padma Shri** in recognition of his contribution to Indian science and technology.Director of the Centre for Cellular and Molecular Biology (CCMB) since 1998, Singh is best known for developing a unique way of DNA fingerprinting that has been accepted by Indian courts as valid in forensic evidence, paternity determination and seed stock verification. This technique was used during the probe into the Rajiv Gandhi murder case. This new technique prompted the government to set up the Centre for DNA Fingerprinting and Diagnostics for further exploration in the field.

Indira Nath (1938 - 2021)

Prof. Nath's (14 January 1938 - 24 October 2021) was an Indian immunologist. **Her major contribution in medical science deals with mechanisms underlying immune unresponsiveness in man, reactions and nerve damage in leprosy and a search for markers for viability of the Leprosy bacillus**. Prof. Nath's fields of specialisations are Immunology, Pathology, Medical biotechnology and communicable diseases. Her research is focused on the cellular immune responses in human leprosy as well as nerve damage in the disease**. Her discovery and her pioneering work are a significant step towards the development of treatment and vaccines for leprosy. She was awarded the Padma Shri by Government of India in 1999**.

Benjamin Peary Pal (1906 – 1989)

B. P. Pal (26 May 1906 – 14 September 1989) was an Indian plant breeder and agronomist who served as a director of the Indian Agricultural Research Institute in Delhi and as the first Director General of the Indian Council of Agricultural Research. **He worked on wheat genetics and breeding but was also known for his interest in rose varieties**. He was elected a Fellow of the Royal Society (FRS) in 1972. He was a bachelor and donated his property to the Indian Council of Agricultural Research. He was awarded the Padma Shri in 1959 and Padma Bhushan in 1968.

Dilip K. Biswas

He is an Indian environmentalist and former chairman of the Central Pollution Control Board and Delhi Pollution Control Committee. He was a member of the panel which conducted ecological studies on Silent Valley and checked the feasibility of a hydro-electric project in the area, eventually recommending against project, leading to the declaration of Silent Valley as a National Park.] He is the author of *Implementation of the Clean Development Mechanism in Asia and the Pacific: Issues, Challenges, and Opportunities*, a report published by the United Nations as a guideline for the implementation of the Clean Development Mechanism (CDM), prescribed by Kyoto Protocol. **His contributions are also reported behind the drafting of the environment management laws in Lucknow, the capital city of the Indian state of Uttar Pradesh**. The Government of India awarded him the fourth highest civilian honour of the Padma Shri, in 2007, for his contributions to science and technology.

Ananda Mohan Chakrabarty (1938 – 2020)

Prof. Chakrabarty genetically engineered a new species of *Pseudomonas* bacteria ("the oil-eating bacteria") in 1971 while working for the Research & Development Center at General Electric Company in Schenectady, New York.

Prof. Chakrabarty discovered a method for genetic cross-linking that fixed all four plasmid genes in place and produced a new, stable, bacterial species (now called *Pseudomonas putida*) capable of consuming oil one or two orders of magnitude faster than the previous four strains of oil-eating microbes. The new microbe, which Chakrabarty called "multiplasmid hydrocarbon-degrading *Pseudomonas*," could digest about two-thirds of the hydrocarbons that would be found in a typical oil spill**. The Government of India awarded him the fourth highest civilian award of the Padma Shri in 1981 and followed it up with the third highest award of the Padma Bhushan in 2006**. **The Western Ghats Ecology Expert Panel (WGEEP), also known as the Gadgil Commission after its chairman Madhav Gadgil, was an environmental research commission appointed by the Ministry of Environment and Forests of India**.

Ancient World Biologist

Anaximander the Milesian (610 - 546 BC)

The pupil of Thales, is often referred to as the first proponent of evolution. Whereas his theories seem very strange when compared to the later work of Charles Darwin, he was the first philosopher to postulate relationships between the various animals and humanity. Many of his exact points concerning the evolution of species and the origins of humanity sound almost comical, but the basic principle and philosophy behind his idea was extremely insightful.

Anaximander noticed that, compared to animals, humans took longer to rear and that children could not find food for themselves. Therefore, humans must have originally originated from another species that could find food for itself and be completely self-sufficient from a young age.

Primitive animals were derived from the moisture evaporated by the heat of the sun and early humans resembled a fish. The animals swimming in the water were protected by a spiny skin and, when they emerged onto the land, this skin split and their behaviors changed to suit the new environment.

Therefore, fish and men were not created at the same time, but fish were first and gave rise to humanity through this process of change. This explains his first point, namely how could humans have arisen if the young cannot fend for themselves.

Hippocrates (460 - 370 BC)

Hippocrates of Kos, also known as Hippocrates II, was a Greek physician of the Age of Pericles (Classical Greece), who is considered one of the most outstanding figures in the history of medicine. He is traditionally referred to as the "**Father of Medicine**" in recognition of his lasting contributions to the field, such as the use of prognosis and clinical observation, the systematic categorization of diseases, or the formulation of humoural theory. The Hippocratic school of medicine revolutionized ancient Greek medicine, establishing it as a discipline distinct from other fields with which it had traditionally been associated and, thus establishing medicine as a profession.

Hippocratic medicine was **influenced by the Pythagorean theory** that Nature was made of four elements (water, earth, wind and fire), and therefore, in an analogous way, the body consisted of four fluids or 'humors' (black bile, yellow bile, phlegm and blood). He is credited with writing fifty books, the important being Aphorism (i) Airs, Waters and Places (ii) Sacred Diseases (iv) The law, The Physician and Oath. His oath for graduate physicians is being administered even today.

Thales (639 - 544 BC)

The first theoretical biologist is considered to be Thales (639-544 BC) although he was mathematician, who proposed that life originated in water. Thales' most famous philosophical position was his cosmological thesis, which comes down to us through a passage from Aristotle's *Metaphysics*.[57] In the work Aristotle unequivocally reported Thales' hypothesis about the nature of all matter – that the originating principle of nature was a single material substance: water. Aristotle then proceeded to proffer a number of conjectures based on his own observations to lend some credence to why Thales may have advanced this idea (though Aristotle did not hold it himself).

Aristotle (384 - 322 BC)

Aristotle has been called "the father of logic", "**the father of biology**", "the father of political science", "**the father of zoology**", "**the father of embryology**", "the father of natural law", "the father of scientific method", "the father of rhetoric", "the father of psychology", "the father of realism", "the father of criticism", "the father of individualism", "the father of teleology", and "the father of meteorology".[Aristotle is best known as one of the most prominent philosophers of all time. He was also an esteemed student of Plato and later became Alexander, The Great's teacher. **Although less known, as a zoologist Aristotle is to be thanked for the first-ever classification of the animal kingdom**.

He proposed that the animal kingdom should be classified as blooded and non-blooded animals along with its respective sub-classifications. The blooded animals are further divided into four-footed, young-bearing, egg-laying animals, fish, and birds. The non-blooded animals are sub-categorized as insects, mollusks, and crabs. Aristotle also wrote seminal zoological works that laid the base for the structured study of zoology for all of its subsequent successors to this day. Those works are De Generatione Animalium, Historia Animalium, and De Partibus Animalium. Aristotle was the first to use empirical methods and techniques in a proto-scientific method. His meticulous methods and record keeping laid out the template for future researchers in the field, namely the later Islamic scholars, who would guard the wisdom of the Greeks and pass it to the Western world. Aristotle wrote a number of treatises based around his study of Zoology. He is also considered the father of Zoology and Biology as well as Embryology..

His major contribution to embryology is **discovering the blastula and development of notochord**. These studies laid down Baer's laws of Embryology and the germ layer theory of development. These laws helped him study the stages of development of the embryo and laid the foundation of modern embryology. His Scala Naturae' is also known as 'Great Chain of Being'. Here Aristotle placed all the creatures known to him in a hierarchy with the simplest creature at the bottom and human beings at the top. This is akin to evolution

Theophrastes (371 - 287 BC)

Theophrastes (371 - 287 BC) certainly earns the title of '**Father of Botany.**' As the pupil and companion of Aristotle, and the man Aristotle chose as his successor, Theophrastes applied Aristotelian empiricism and meticulous methodology to the study of plants. In two works, '**Enquiry into Plants**' and '**On the Causes of Plants**,' he made the first systematic study of the plant world, in exactly the same way that his mentor categorized animals. He attempted to classify over 500 plants into trees, shrubs, undershrubs and herbs and, whilst he was not entirely successful in this, he certainly understood which features of plants were necessary for making distinctions. His famous books are Historia Plantarum and De Causis Plantarum'. His work was carried forward by Pliny the Elder (28-79 AD). He wrote a book "Historia Naturalis" where he mentions more than 1000 economic plants.

Galen (131-200 AD)

Aelius Galenus or Claudius Galenus (Galen) of Pergamon was a Greek physician, surgeon and philosopher in the Roman Empire, Considered to be one of the most accomplished of all medical researchers of antiquity and was the most famous medical man who established the anatomy of man. Galen influenced the development of various scientific disciplines, including anatomy, physiology, pathology, pharmacology and neurology, as well as philosophy and logic. **His book Anatomical Preparations remained standard medical text for some 1400 years (the longest run for any text book in the world**.

Emergence of Contemporary Biology

The applied study of biology began in and after the 16th century due to inventions of biotechniques, new theories and discoveries of biological facts. Therefore contemporary biology began in the 16th century. The main contributors are highlighted here-

Andreas Vesalius (1514-1564)

After Galen Andreas Vesalius, a Belgium scientist reinvestigated human anatomy. He pointed out a number of drawbacks in Galen's work. He found the human body to be made up of many complex subsystems with each subsystem having its own functions. **Andreas Vesalius is also called 'Father of Anatomy'**. He wrote the book on the structure of the human body in **1543 De Humani Corporis Fabrica'**.The *Fabrica* included illustrations of male and female anatomy. It also included diagrams of uteruses with intact fetuses. Vesalius was one of the first physicians to accurately record and illustrate human anatomy based on his findings from autopsies and dissections, which led to improved understanding of the human body and enhanced surgery techniques.

William Harvey (1578-1657)

William Harvey, a British scientist, found blood circulation with the discovery that blood is pumped by alternate contraction and expansion of heart. His monograph is known as 'Anatomical Exercise on the Motion of Heart and Blood'. Harvey also studied reproduction and embryonic development of chick. While his published work on the circulation of blood is considered the most important of his academic life, **Harvey also made significant contributions to embryology with the publication of his book *Exercitationes de Generatione Animalium* in 1651**. In this book he established several theories that would set the stage for modern embryology and addressed many embryological issues including conception, embryogenesis, and spontaneous generation.

Robert Hooke (1635-1703)

Robert Hooke, a British scientist observed a number of small compartments or cellulae (Micrographia, 1665) in a thin slice of cork under his self-made simple microscope. His cellulae were later on called cells.

Antony Van Leeuwenhock (1632-1723)

Real living cells were observed in 1670 by a Dutch cloth merchant and an amateur lens grinder, Antony Van Leeuwenhock (1632-1723). **Under his simple but powerful microscope he observed bacteria, Euglena, ciliates, sperms, eggs, blood corpuscles, compound eyes of insects and many other structures**. The same were drawn and sent to the "Royal Society of London' for interpretation.

Most of the "animalcules" are now referred to as unicellular organisms, although he observed multicellular organisms in pond water. He was also the first to document microscopic observations of muscle fibers, bacteria, spermatozoa, and blood flow in capillaries. Van Leeuwenhoek did not write any books; his discoveries came to light through correspondence with the Royal Society, which published his letters.

Carolus Linnaeus (1707-78)

Carolus Linnaeus was a Swedish Naturalist who took up the work of nomenclature and classification of organisms. He is known as the ' **Father of Taxonomy**'. After Aristotle and Theophrastus, Linnaeus classified animals and plants on the basis of their comparative morphol- ogy. He published 'Species Plantarum' in 1753 describing about 6000 (actually 5900) species of plants. Linneaus described more than 4000 (actually 4326) species of animals in another book Systema Naturae (1758). Linnaeus is also known as **the father of binomial nomenclature**. He invented this method of nomenclature (1735, 1751) in which every organism is given a scientific name of two words, e.g., **Homo sapiens** (Human), **Pisum sativum** (Pea).

Linnaeus was a strong influence for many famous philosophers and writers, including Jean Jacques Rousseau, who considered him to be the greatest man on Earth. One of his most prominent works, **Systema Naturae**, where he introduced his taxonomy, was first published in the Netherlands.

Georges Leopold Cuvier (1769-1832)

From Aristotle to Linneaus, scientists believed in the fixity of species, i.e., all creatures remain unchanged since their creation as per Wisdom of God'. It was Georges Leopold Cuvier (1769-1832) who found that various periods witnessed different types of fossils. Cuvier identified the fossils of bird-like reptiles. **He laid the foundation of science of fossils or palaeontology. Besides he made contributions in the field of comparative anatomy and as an important contributor to vertebrate paleontology and geology.**

Moreover, Cuvier constructed a system of classification based on specific and well-articulated principles to help anatomists classify animal taxa. Cuvier's opinions influenced the development of biology in France, and his arguments against transmutation of types influenced the reception of Charles Darwin's theory of evolution by natural selection among many French naturalists.

Jean-Baptiste Lamarck (1774 – 1829)

Jean Baptiste Lamarck (1744-1829), a French naturalist, **was the first scientist to propound the idea of evolution in his book Philosophie Zoologique**'. However, he could not give any convincing proof of the same.

Lamarck started as a botanist, but after he was given an invitation to join the Jardin des Plantes, he became a zoologist. Even though most will associate his name with the ideas behind organic evolution, he has made significant and plentiful contributions to zoology in general. **It is also less known that Lamarck was almost a predecessor of Schwann and Schleiden concerning their cell theory,** as he came very close to defining it nearly 40 years before them.The modern era generally remembers Lamarck for a theory of **inheritance of acquired characteristics,** called **Lamarckism** (inaccurately named after him), soft inheritance, or use/disuse theory,[7] which he described in his 1809 ***Philosophie Zoologique***. However, the idea of soft inheritance long antedates him, formed only a small element of his theory of evolution, and was in his time accepted by many natural historians. Lamarck's contribution to evolutionary theory consisted of the first truly cohesive theory of biological evolution.

Charles Darwin (1809 – 1882)

Charles Robert Darwin (1809-82) collected a large amount of evidence that helped him to propose that species arise through changes or evolution governed by their natural selection. **The conclusions were published in 1859 in his book, ``On the Origin of Species by Means of Natural Selection: The Preservation of Favoured Races in the Struggle for life."**

According to Darwin, all species have come from a common ancestor and have evolved through the process of natural selection. His continuous insights and studies on different classes of animals have resulted in an immense collection of data, which was later published through his books.One can imagine Darwins surprise and the pain of his inner conflict when, after working for 20 years on his theory, he received a package from Indonesia in 1858 containing an essay written by the young English naturalist Alfred Russell Wallace containing an outline of a theory nearly identical to his own, which Wallace indicated was devised one night during a malarial fit. Although both men are credited with the theory of natural selection, priority for the idea of natural selection -- the essence of the theory -- cannot be denied to Darwin, as he had recorded his ideas to paper in 1838 when Wallace was still a teenager. Altogether, **Darwin wrote 14 books, in addition to 4 monographs on the taxonomy and biology of barnacles, and his narrative of the Voyage of the Beagle**. After Darwin had written down his ideas in his long paper of 1844. In 1868 Charles Darwin proposed **Pangenesis**, a developmental theory of heredity. In 1871 his book **The Descent of Man was** published, in which he argued that humans were no different from all other forms of life, and that we too, in our evolutionary history, have been influenced by the forces of natural selection. Then, in **The Expression of the Emotions in Man and Animals**, published in 1872, he dared to claim that most of our refined and most particularly human behavior -- the expression of our emotions -- also reflected our evolutionary past.

Alfred Russel Wallace (1823 – 1931)

Before Darwin, Wallace was the one who came up with his own theory of natural selection. It was his work that influenced Darwin and his Theory of Evolution. He is regarded as **the father of biogeography** due to his research on the basin of the river Amazon. He defined a line (called the **Wallace Line**) that separates the Indonesian archipelago in areas containing species of Australian origin and those of Indian origin.

Robert Brown (1773 –1858)

Brown, was a Scottish botanist and paleobotanist who made important contributions to botany largely through his pioneering use of the microscope. His contributions include one of the earliest detailed descriptions of the **cell nucleus** and cytoplasmic streaming; the observation of Brownian motion; early work on plant pollination and fertilisation, including being the first to recognise the fundamental difference between gymnosperms and angiosperms; and some of the earliest studies in palynology. He also made numerous contributions to plant taxonomy, notably erecting a number of plant families that are still accepted today; and numerous Australian plant genera and species, the fruit of his exploration of that continent with Matthew Flinders. In 1831, while investigating the fertilization mechanisms of plants in the Orchidaceae and Asclepiadaceae families, he noted the existence of a structure within the cells of orchids, as well as many other plants, that he termed the “nucleus” of the cell.

Félix Dujardin (1801 – 1860)

Dujardin was a French biologist born in Tours. He is remembered for his research on protozoans and other invertebrates. His studies of infusoria (microscopic animal life frequently found in infusions of decaying organic materials) led Dujardin in 1834 to propose a new group of one-celled animals (called protozoans) that he called the Rhizopoda (meaning “rootfeet”). In the group Foraminifera, he observed the seemingly formless life substance that exuded outward through openings in the calcareous shell and **named the substance sarcode, later known as protoplasm**. This work led him in 1835 to refute the theory (reintroduced by Christian Ehrenberg) that microscopic organisms have the same organs as higher animals. He also studied cnidarians (*e.g.,* jellyfish and corals) and echinoderms (*e.g.,* starfish); **his study of helminths (flatworms) laid the foundation for the later development of parasitology.**

Theodor Schwann (1810 – 1882)

Schwann was a German physician and physiologist. **His most significant contribution to biology is considered to be the extension of cell theory to animals**. Other contributions include the discovery of Schwann cells in the peripheral nervous system, the discovery and study of pepsin, the discovery of the organic nature of yeast, and the invention of the term metabolism.

Matthias Schleiden (1804-1881)

Matthias Jacob Schleiden helped develop the cell theory in Germany during the nineteenth century. Schleiden studied cells as the common element among all plants and animals. Schleiden contributed to the field of embryology through his introduction of the Zeiss microscope lens and via his work with cells and cell theory as an organizing principle of biology.

Cell Theory

The classical cell theory was proposed by Theodor Schwann in 1839. There are three parts to this theory. The first part states that all organisms are made of cells. The second part states that cells are the basic units of life. These parts were based on a conclusion made by Schwann and Matthias Schleiden in 1838, after comparing their observations of plant and animal cells. The third part, which asserts that cells come from preexisting cells that have multiplied, was described by Rudolf Virchow in 1858, when he stated *omnis cellula e cellula* (all cells come from cells).

Rudolf Carl Virchow (1821-1902)

Rudolf Carl Virchow lived in nineteenth century Prussia, now Germany, **and proposed that *omnis cellula e cellula***, which translates to each cell comes from another cell, and which became a fundamental concept for cell theory. **He helped found two fields, cellular pathology and comparative pathology, and he contributed to many others. Ultimately Virchow argued that disease is caused by changes in normal cells, also known as cellular pathology**.

Louis Pasteur (1822 – 1895)

Pasteur was a French chemist and microbiologist **renowned for his discoveries of the principles of vaccination, microbial fermentation, and pasteurization**. His research in chemistry led to remarkable breakthroughs in the understanding of the causes and preventions of diseases, which laid down the foundations of hygiene, public health and much of modern medicine. His works are credited to saving millions of lives through the developments of vaccines for rabies and anthrax. **He is regarded as one of the founders of modern bacteriology and has been honoured as the "father of bacteriology and as the "father of microbiology (together with Robert Koch, and the latter epithet also attributed to Antonie van Leeuwenhoek**.

Pasteur was responsible for disproving the doctrine of spontaneous generation. Under the auspices of the French Academy of Sciences, his experiment demonstrated that in sterilized and sealed flasks, nothing ever developed; and, conversely, in sterilized but open flasks, microorganisms could grow.

Heinrich Hermann Robert Koch (1843 – May 1910)

Robert Koch was a German physician and microbiologist. **As the discoverer of the specific causative agents of deadly infectious diseases including tuberculosis, cholera (though the bacterium itself was discovered by Filippo Pacini in 1854), and anthrax, he is regarded as one of the main founders of modern bacteriology. As such he is popularly nicknamed the father of microbiology (with Louis Pasteur[3])**, and as the father of medical bacteriology. His discovery of the anthrax bacterium (*Bacillus anthracis*) in 1876 is considered as the birth of modern bacteriology. His discoveries directly provided proofs for the germ theory of diseases, and the scientific basis of public health

While working as a private physician, Koch developed many innovative techniques in microbiology. He was the first to use oil immersion lens, condenser, and microphotography in microscopy. His invention of bacterial culture method using agar and glass plates (later developed as the Petri dish by his assistant Julius Richard Petri) made him the first to grow bacteria in the laboratory. In appreciation of his works, he was appointed as government advisor at the Imperial Health Office in 1880, promoted to a senior executive position (*Geheimer Regierungsrat*) in 1882, Director of Hygienic Institute and Chair (Professor of hygiene) of the Faculty of Medicine at Berlin University in 1885, and the Royal Prussian Institute for Infectious Diseases (later renamed Robert Koch Institute after his death) in 1891.

Gregor Johann Mendel (1822-84)

Mendel is rightly called the **Father of Genetics**. His work remained unnoticed till 1900. The Austrian monk, Gregor Johann Mendel, discovered the basic laws of heredity and laid the foundation for the science of modern genetics. The importance of his work was not recognised until 1900, 12 years after Mendel's death and 34 years after its publication. His childhood experience of horticultural work as the son of a peasant farmer had given him an interest in the role of hybrids in evolution. Much of his work was performed on the edible pea, which he grew in the monastery garden. Between 1856 and 1863 he cultivated and tested at least 28 000 pea plants, carefully analysing pairs of contrasting traits (such as plant tallness, flower colour, seed shape, pod shape, and flower position on the stem) that appeared in different pea plant progeny. From his findings, Mendel concluded that each plant contributed a factor that determines a particular trait and that pairs of factors in the offspring do not give rise to an amalgamation of traits. These conclusions, in turn, led him to formulate his laws of segregation and the law of independent assortment of characters, which are now recognised as two of the fundamental laws of heredity.

He noted that various traits were inherited as separate units, each of which was inherited independently of the others. He suggested that each parent has pairs of units but only one unit from each pair contributed to the offspring. The units that Mendel described were later named genes. The word gene was coined in 1906 by the British biologist William Batson.

In 1900, three investigators, K E Correns of Germany, E Tshermak von Seysenegg of Austria, and Hugo de Vries of The Netherlands independently obtained results similar to Mendel's and after searching the scientific literature, located his original reports. Fame only came to him after his death.

August Weismann (1834–1914)

Friedrich Leopold August Weismann published *Das Keimplasma: eine Theorie der Vererbung* (*The Germ-Plasm: a Theory of Heredity*, hereafter *The Germ-Plasm*) while working at the University of Freiburg in Freiburg, Germany in 1892. William N. Parker, a professor in the University College of South Wales and Monmouthshire in Cardiff, UK, translated *The Germ-Plasm* into English in 1893. In *The Germ-Plasm*, Weismann proposed a theory of heredity based on the concept of the germ plasm, a substance in the germ cell that carries hereditary information. *The Germ-Plasm* compiled Weismann's theoretical work and analyses of other biologists' experimental work in the 1880s, and it provided a framework to study development, evolution and heredity. Weismann anticipated that the germ-plasm theory would enable researchers to investigate the functions and material of hereditary substances.

The Germ-Plasm provided hereditary explanations for developmental and evolutionary phenomena. *The Germ-Plasm* has an introduction and four parts, divided into fourteen chapters.

Table - Important Contributions in Biology Since 1900

S.No.	**Scientist**	**Year**	**Contribution**
1.	Hugo de Vries (1848-1935), Dutch genetist. (11) Erich von Tschemak-Seysenegg (1871-1962), Austrian genetist. (iii) Karl Correns (1864-1933), German genetist.	1900	Rediscovered Mendel's work. Beginning of Genetics
2.	Walter Sutton (1877-1916), American	1904	Studied chromosomes and proposed chromo- somal basis of heredity.
3.	William Bateson (1861-1926), British biologist	1905, 1909	Coined the term genetics, discovered linkage, complementary genes and conducted experi- ments to reinforce the idea that each trait is controlled by a different gene.
4.	Thomas Hunt Morgan (1866-1945) American geneticist	1910-1930	Studied criss-cross inheritance, linkage, crossing over. over and prepared first gene maps showing linear arrangement of genes along the chromosome. Wrote a book, The theory of gene (1926)'
5.	Alexander Fleming (1881-1955), as British bacteriologist	1928	Discovered the first antibiotic penicillin He found that in his culture of Staphylococcus, the bacteria got killed where it was contaminated with fungus Penicillium notatum. The drug was used successfully in treating soldiers during world war II.
6.	Oswald Theodore Avery (1877-1955)	1944	Alongwith Macleod and McCarty, found genes to be composed of DNA. Since then DNA has become the focus of genetists.
7.	Alongwith Macleod and McCarty, found	1953	Discovered double helical structure of DNA (coil of life), ushered in a new era of Molecular Biology
8.	Har Gobind Khorana (1922 Indian born in Raipur (Pakistan), later American biochemist. (i) Robert W. Holley (1922-1993). American scientist. i) Marshall W. Nirenberg (1927-), American Scientist.	1968	Awarded Nobel Prize jointly "for their interpretation of the genetic code and its role in protein synthesis". Khorana synthesised oligonucleotides and produced the first man-made gene in early 1970s. These artificial genes are now widely used in sequencing, cloning and engineering new organisms. Concept of genetic code has helped in indepth under- standing of different aspects of biology at molecular level
9.	Norman Ernst Borlaug (1914-), American agronomist		
10.	Stanley Cohen (1922-). (ii) Herbert Boyer (1936). Both American biochemist		Discovered rDNA (recombinant D) technology which has given birth to modern biotechnology. Insulin for treating diabetes is being produced by genetically engineered bacteria. A defective gene can now be re- paired and replaced by a normal gene. Geneti- cally modified (GM) crops are now being produced.
11.	Ian Wilmut (1944-)	1996	Created the first boar calf, Frosty from a frozen embryo. In 1996, Wilmut and Campbell produced the first animal clone, a Finn Dorset Lamb, Dolly (born February 1997) by replacing the nucleus of egg with nucleus from a differentiated adult mammary (udder) cell.
12.	U.S. Department of Energy and National Institute of Health	2001	Launched Human Genome Project or HGP in 1990. Found it to contain over 3.0 (3.2) billion base pairs on June 26, 2000. Draft of Human Genome was published in February 2001. It has about 30,000 genes. The same are being identified.
13.	The Human Genome Project (HGP)	2003	Completed in April 2003, the HGP gave us the ability, for the first time, to read nature's complete genetic blueprint for building a human being.